STRENGTHS AND LIMITATIONS OF BENEFIT-COST ANALYSES
APPLIED TO THE ASSESSMENT OF INDUSTRIAL
ORGANIC CHEMICALS INCLUDING PESTICIDES

MONOGRAPH VI

QUANTITATIVE ESTIMATION OF THE RISK TO HUMANS RESULTING FROM EXPOSURE TO CHEMICALS

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NATIONAL RESEARCH COUNCIL OF CANADA
NRCC ASSOCIATE COMMITTEE ON SCIENTIFIC CRITERIA
FOR
ENVIRONMENTAL QUALITY

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by

M.F. Mitchell, E. Vavasour, P.B. Curry and J.R. Roberts

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ABSTRACT

This monograph presents a methodology for ranking the relative human risks from several toxic chemicals and for analyzing the errors inherent to each risk estimate. The methodology consists of estimating the level of human exposure and dose of a chemical and the probability of an adverse effect being manifested at that dose.

The authors critically review current methods for measuring and estimating exposure and summarize a similar analysis of methods for estimating risk (Willes et al. 1985). They clearly identify the advantages and limitations of the methodology developed in this monograph.

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Mitchell, M.F., Vavasour, E., Curry, P.B., and Roberts, J.R. 1987. Quantitative estimation of the risk to humans resulting from exposure to chemicals. Monograph VI In Strengths and Limitations of Benefit-Cost Analyses Applied to the Assessment of Industrial Organic Chemicals Including Pesticides. Associate Committee on Scientific Criteria for Environmental Quality. National Research Council of Canada. NRCC No. 24465.

RÉSUMÉ

On présente une méthodologie pour coter les dangers que représentent pour l'homme divers produits chimiques toxiques et pour analyser les erreurs inhérentes à toute estimation de risque. La méthodologie comprend l'estimation du taux d'exposition de l'homme et de la dose du produit chimique, ainsi que de la probabilité d'un effet néfaste à cette dose.

Les auteurs passent en revue les méthodes actuelles permettant de mesurer et d'estimer l'exposition et ils donnent un résumé d'une analyse semblable des méthodes à partir desquelles on peut estimer le danger (Willes et al. 1985). Ils mettent en relief les avantages et les limitations de la méthodologie mise au point dans cette monographie.

CITATION

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MANDATE OF THE ASSOCIATE COMMITTEE ON SCIENTIFIC CRITERIA FOR ENVIRONMENTAL QUALITY

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The Associate Committee's program includes the evaluation of available information on the probability of effects of contaminants on receptors together with the related fundamental principles and scientific knowledge. In this work particular attention is directed to receptors and contaminants (and their interactions) important to Canada. This Canadian approach is necessary because evaluations made in other countries or regions will not always be applicable to the particular circumstances prevailing in Canada.

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TERMS OF REFERENCE OF THE SUBCOMMITTEE ON PESTICIDES AND INDUSTRIAL ORGANIC CHEMICALS

(1) The preparation of reports critically evaluating and collating the available cause-effect relationships, which permit the estimation of the environmental risks associated with the use of synthetic organic chemicals in Canada -- these documents provide criteria for the evaluation of both present and future use patterns, and

(2) the identification of gaps in available criteria and preparation of recommendations for future research in these areas.

To meet this mandate, the Subcommittee identified a number of priority compounds for consideration. Comprehensive reports were prepared to bring into perspective the diverse and somewhat obscure observations found in the literature. The documents consisted of reviews, summarizing the available criteria and the research required. They also contained, as supporting material, the available data on which the overview is based.

The mandate of the Subcommittee did not include the setting of objectives and standards, the development of risk assessment, or the establishment of registered uses for pesticides in Canada. Therefore, it did not permit consideration of the engineering or legal aspects. The Subcommittee was only concerned with scientific information and environmental criteria. The documents did provide one of the components necessary in the consideration and development of risk assessments. Other agencies, both federal and provincial, have the actual responsibility for making decisions about the uses of specific synthetic organic chemicals in Canada, and hence they have the task of bringing about an acceptable balance between the risks and benefits associated with the use of such chemicals by our society.

As of 1 April 1985, the activities of the Subcommittee ceased. This action represents a shift in government priorities and economic considerations.

PREFACE

The need to establish the balance between the benefits gained and the costs incurred by society from the use of organic chemicals is a central theme in current discussions about the regulation of organic chemicals. Although it is agreed that the basis of benefit-cost analyses and the approach for their application to the problems of regulating organic chemicals is well developed in theory, the actual application of this methodology and the identification of the associated strengths, limitations, and errors have seldom occurred.

At the request of Agriculture Canada, the National Research Council of Canada undertook to produce a comprehensive analysis of the usefulness of benefit-cost analyses for developing defensible regulatory decisions. Pesticides were chosen as a case study because they have one of the best-developed data bases.

Experts in epidemiology, toxicology, health costs, agriculture, and economics developed a consensus on the general strengths and problems of applying benefit-cost methodology to issues surrounding the regulation of pesticides. They developed three specific case studies to test the methodology and to determine the overall accuracy of the results in real situations. The case studies examine the use of the fungicide captan in strawberries, the insecticide fonofos in onions, and the herbicides 2,4-D and 2,4,5-T for conifer release in forestry.

The views of these experts are published in the following series of monographs:

Monograph I
Framework for the Application of Benefit-Cost Analyses to the Assessment of Industrial Organic Chemicals.

The utility and role of benefit-cost analyses within the decision-making process are examined.

Monograph II
Epidemiologic Evidence of the Effects of Pesticides on Human Health in Canada.

The feasibility of using epidemiologic approaches to establish the incidence rate of diseases associated with organic chemicals is examined within the Canadian context. Also examined are Canadian data sources for characterizing the critical groups.

Monograph III

Extrapolation of Toxicological Data from Laboratory Studies to the Human Situation.

Errors associated with developing extrapolations from laboratory studies to the human situation are examined.

Monograph IV

Evaluation of Costs Associated with Human Health Impacts.

The utility of welfare-accounting and output-accounting methodologies to the costing of the health outcomes associated with organic chemicals is examined. Also, the usefulness of Canadian data on health costs is analyzed within the context of the needs of these methodologies.

Monograph V

Evaluation of the Biological and Economic Benefits of Pesticide Use.

Methodologies for characterizing the yield and economic benefits from the use of pesticides are identified. The data necessary to develop economic estimates are examined to characterize the errors inherent in the process.

Monograph VI

Quantitative Estimation of the Risk to Humans Resulting from Exposure to Chemicals.

Various models for characterizing exposure and incidence rates as well as the role of the models in benefit-cost analysis are analyzed in detail. A Monte Carlo technique is used to characterize the uncertainty around the prediction of incidence rates from laboratory studies. Unfortunately, the authors were unable to complete this project because of the discontinuation of the activities of the Environmental Secretariat. After reviewing the document, the Associate Committee on Scientific Criteria for Environmental Quality felt that there was value in its publication, even though it is incomplete.

Some of these monographs include extensive analysis of methodologies and do not follow the usual format of NRCC criteria monographs. They are published in the criteria monograph series because the information and analysis that they contain are critical to assessing the usefulness of benefit-cost analysis.

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1.0 INTRODUCTION

Toxic chemicals are ubiquitous in our environment. It is impractical to discontinue the use of all such chemicals, and, even if the release of a chemical to the environment is discontinued, the eradication of environmental residues can be extremely difficult. The use of a chemical or the costs of extensive cleanup operations can best be justified through benefit-cost analysis.

The National Research Council of Canada has developed a methodology for estimating the relative costs and benefits associated with a chemical's use. This methodology includes computer models for estimating human exposure, short- and long-term human health risks, associated economic costs and the economic benefits resulting from the chemical's use in a specific situation. These estimates may then be combined to predict the net cost or benefit resulting from the use of a chemical. However, such analysis requires data that, at present, are usually inadequate. This is particularly true of the risk component of the analysis.

Benefit-cost estimations are of very limited use unless the associated errors and variability are defined. A novel component of the NRCC methodology is the use of Monte Carlo statistics to predict a set of possible solutions, by random sampling from the range of values input for each parameter used in the estimations, over a number of iterations. Statistical analysis then yields a range of likely answers, each with an estimated probability of occurring. The results are combined to estimate the net cost or benefit as a distribution of probable answers, reflecting the variability in all the parameters involved.

The methodologies for estimating human exposure and the risks to human health are discussed in this document. The estimation of the economic costs of health effects is discussed by Victor (1985), and the estimation of economic benefits resulting from pesticide use is discussed by Roberts, Lloyd *et al.* (1985).

Predictions of the human health risk associated with the use of a chemical are based on the level of exposure to the chemical, the number of people exposed and the probability of a health effect occurring at that exposure level. Errors arise in determining each of these factors.

Human exposure and dose may be estimated on the basis of actual measurements, or predicted from models. The identification of critical groups at risk and the estimation of the total number of people exposed in a particular situation are discussed by Roberts, Curry *et al.* (1985) and in Chapter 4. Predicting the probability of a health effect being manifested at a particular exposure level is discussed in Chapter 3 and by Willes *et al.* (1985).

In the extrapolation of risk to humans, there is a temptation to err on the side of safety by the exclusive use of "worst-case" estimates. Although this may be prudent for regulators attempting to establish "safe" exposure levels associated with acceptable risk levels, it is inconsistent with the basic philosophy of benefit-cost analysis. Such worst-case estimates do not define errors and may not reflect reality, whereas the use of Monte Carlo techniques allows the definition of the most probable "accurate" value with a specified error. This facilitates ranking of the relative impacts of several toxic compounds, and is consistent with the overall NRCC methodology for benefit-cost analysis.

Predictions of exposure are made for three case-study situations: captan as applied to strawberries in British Columbia; fonofos as applied to onions in southern Ontario; and 2,4-D/2,4,5-T as applied for conifer release in New Brunswick (Chapter 5). A case-study risk analysis for captan is detailed in Chapter 6. The risk analysis is included solely to demonstrate the techniques for estimating risk. Because of government constraints, the authors had time only to partially validate the methodology as described in Appendix II.0. As well, the available data are inadequate in most cases. As a result, the exposure and risk estimates may not be generally applicable and should be quoted only in the context of this document. They are useful only as examples of how the methodology may be used.

2.0 OVERVIEW AND RECOMMENDATIONS

A methodology to estimate human exposure and health risks associated with a chemical's specific use was developed as part of a computer package[a] designed to facilitate benefit-cost analysis. The methodology includes a comprehensive analysis of the errors inherent to such estimates.

It must be emphasized that the methodology is currently of little practical use for regulatory purposes. It has many inadequacies because of deficiencies in the present state of extrapolative theories and techniques, the lack of knowledge of basic toxic mechanisms and gaps in specific data bases. The individual computer modules were carefully debugged and partially validated (Appendix II.0), but government constraints meant the authors were unable to complete their work on this methodology and to fully evaluate its accuracy. However, the basic design of the methodology is thought to be an improvement on current approaches, specifically because errors in estimations can potentially be defined. As our knowledge increases, it should be possible to refine this methodology so that it could be used by regulators. In particular, it could become an extremely useful screening tool for estimating the relative risks of chemicals. Meanwhile, the risk estimates generated should be considered only to demonstrate how the methodology can be used and the magnitude of the errors on the estimates. The risk estimates should not be cited in any other context.

The methodology consists of two parts: estimating the level of human exposure and dose of a chemical, and estimating the probability of an effect occurring at that dose.

2.1 ESTIMATING HUMAN EXPOSURE AND DOSE

Current methods for measuring and estimating exposure, including existing predictive models, have been critically reviewed, and an attempt has been made to quantify the errors associated with these methodologies. Such errors arise from variations in environmental, biological and behavioral factors, as well as from methodological limitations. It was found that, whereas some of these variables could be quantified, most studies either do not consider or do not report all the factors which determine their bias. Analysis of the errors inherent to most exposure measurements is thus impossible. This lack of basic data also reduces the usefulness of studies by making it difficult to extrapolate the results to different situations.

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[a] The computer package is written in BASIC for use with the IBM-PC. It is not available for distribution.

2.2 ESTIMATING HUMAN DISEASE INCIDENCE RATES

Because toxicity data are usually gathered from studies using laboratory animals that have been subjected to relatively high doses of chemicals, predicting human risk involves extrapolating between species, between dose levels and often between dosing routes and regimes. An in-depth analysis of toxicological extrapolation is carried out in Willes et al. (1985).

There is often considerable variation in response between and even within species. As well, the relationships between disease states monitored in animals and those diagnosable in humans are not always well defined. The most easily quantified pathological parameters are changes in basic physiology and biochemistry, but it is often difficult to relate effects on such parameters to disease.

As well as usually being subjected to relatively high doses of chemicals, laboratory animals are subjected to specific dosing regimes which often do not reflect human exposure patterns. Our understanding of the pharmacodynamics and mechanisms of action of most chemicals is too limited at present to compare different dosing regimes. Similar problems are encountered in attempting to compare dosing routes.

A range of models is available for extrapolating from a response at a high dose to a response at a lower dose, i.e. for predicting the shape of the dose-response curve at low doses. The predictions from these models can vary by five or six orders of magnitude, and, for most data sets, it is impossible to determine which model is best on statistical grounds alone. For some chemicals it is possible that there is a threshold dose below which effects would not be observed; in such cases, the errors in predicting effects at doses below the threshold would be zero as, by definition, there would be no effect. However, for most compounds, data are inadequate to predict whether a threshold is theoretically likely, much less what its value is.

2.3 RECOMMENDATIONS

(1) HUMAN EXPOSURE STUDIES SHOULD BE DESIGNED SO THAT RESULTING ESTIMATES CAN BE VALIDATED AND ERRORS ASSESSED. BASIC DATA SHOULD BE INCLUDED IN PUBLICATIONS TO FACILITATE EXTRAPOLATION OF THE DATA TO OTHER SITUATIONS.

(2) ONE FOCUS NEEDED IN TOXICOLOGY RESEARCH IS THE IMPROVEMENT OF ANIMAL STUDY PROTOCOLS AND ANALYSES SO THAT THE ERRORS IN EXTRAPOLATING TO HUMANS COULD BE REDUCED. IN THE DESIGN OF PROTOCOLS, THIS MIGHT INVOLVE:

(a) BETTER DEFINING THE DOSE-RESPONSE CURVE THROUGHOUT THE OBSERVABLE RANGE; AND

(b) ANALYSIS OF MECHANISMS OF ACTION TO FACILITATE SELECTION OF APPROPRIATE TEST SYSTEMS, DOSAGE ROUTES AND DOSAGE REGIMES.

IN THE ANALYSES OF ANIMAL TESTS, THIS COULD ALSO INVOLVE THE DEVELOPMENT OF AN OBJECTIVE BASIS FOR DISCRIMINATION BETWEEN METHODS OF EXTRAPOLATION, PARTICULARLY TAKING ACCOUNT OF ANY MECHANISTIC JUSTIFICATION FOR THE CONCEPT OF A THRESHOLD DOSE FOR TOXIC EFFECTS.

3.0 GENERAL DISCUSSION ON PREDICTING HUMAN RISK

There are two general approaches to predicting the risk resulting from the exposure of humans to chemicals. The first involves epidemiological studies that attempt to establish specific correlations between exposure to chemicals and human disease. Roberts, Curry et al. (1985) concluded that this approach is seldom useful for generating disease incidence rates for specific chemicals because of confounding factors (e.g. exposure to multiple chemicals) and because the statistical power of most studies is too low. Another limitation of this approach is that it seldom yields information in advance of widespread human exposure to a chemical. Because a response must usually be either catastrophic or very specific to be detected, this is obviously not satisfactory.

The second approach is to predict human risk from toxicity data gathered on a variety of non-human test systems. This involves extrapolating between, as well as within, species, and usually from high to low dose levels and between different dosing regimes. This approach is discussed here.

A first step in quantitative risk estimation is defining the incidence rate for the disease in a population. The background incidence rate (I) is defined as:

$$I = \frac{\text{Number of individuals with the disease in a population}}{\text{Total population}}$$

Where the incidence rate of concern is for an effect caused by a specific chemical, it can be expressed for a particular dose (d) of the chemical as:

$$I(d) = \frac{\text{Number of individuals showing effect in dose group}}{\text{Total in dose group}} - I$$

3.1 EQUATING DISEASE BETWEEN SPECIES

Disease states monitored in animal studies and those diagnosable in humans must be compared, but the relationships are seldom well defined. For example, animal studies often document non-malignant tumors, precancerous lesions, organ hyperplasia, etc., as well as true malignant tumors. In such cases, the extrapolation to humans involves an at least partially subjective decision as to which observed effects are likely to equate with what would be diagnosed as cancer in humans.

Errors in predicting the type or severity of response in humans could influence the accuracy of benefit-cost analysis. There are few data to support the assumption that specific tumor sites and types

or the site of a teratogenic effect in laboratory animals would be the same in humans. Many terata of the skeletal structure cannot be directly compared, as the same appendages may not even be present in different species (e.g. tail). In laboratory rodents there is a high background incidence of mild aberrations that do not have known functional significance (e.g. supernumerary ribs). Such effects may not be diagnosed if they occur in humans.

A common effect of chemicals in laboratory rodents is increased resorption of fetuses. Even assuming such resorptions can be equated to natural abortions in humans, the time factor of the resorption/abortion relative to the gestation period must be considered. In humans this could affect whether the problem is diagnosed as infertility or miscarriage, resulting in quite different estimates of economic costs. The high background incidence of resorptions/abortions is another confounding factor.

Laboratory animals bear litters, whereas humans usually carry one fetus per pregnancy. The variation in data between litters is usually greater than that within litters. How the data are pooled can affect predicted incidence rates. The extrapolated incidence rate will also vary depending on whether abortions per pregnancy or abortions per litter are considered to represent the incidence rate in animals, i.e. whether the effect is considered to be on the mother or on the offspring. Although maternal effects are generally examined, it is unclear which is the more relevant datum. This problem also applies to estimating the incidence of stillbirths and neonatal deaths.

Whereas human diseases are usually diagnosed as a quantal (all-or-nothing) response, the biological responses that result in the disease are usually quantitative (i.e. of varying degrees of severity). Often, it is such quantitative physiological or biochemical parameters that are measured in laboratory studies. Because extrapolation models generally handle only quantal data, quantitative data must be converted to approximate quantal data. It may be possible to define the minimum change in a biochemical or physiological parameter that equates with a symptom or disease. In such a case, the incidence rate could be defined as:

$$I = \frac{\text{Number of animals with } >X\% \text{ change in parameter}}{\text{Total number of animals in group}}$$

An example that illustrates these points is the acetylcholinesterase (CHO) inhibition caused by many organophosphorous and carbamate pesticides. A decrease in CHO activity can cause neurological abnormalities, one of the most common acute reactions to pesticides observed in humans. In animals, CHO inhibition is assayed in plasma, red blood cells and brain tissue. Apparently, effects are manifested only above a minimum level of inhibition of CHO.

3.2 EQUATING DOSING REGIMES

Differences between the dosing regimes used in laboratory studies and patterns of human exposure can affect the accuracy of the incidence rates predicted for humans from laboratory animal studies.

In chronic laboratory studies, animals are usually dosed over a major portion of their life span. Humans are often exposed for only a relatively short period, but the general population can be exposed over longer periods through food residues. In acute studies, the dosing period is short and defined in the laboratory, but humans may be subjected to spasmodic or repeated periods of dosing.

To attempt to equate such differences, it is necessary to predict how toxic effects might cumulate over the time scale of dosing. This requires an understanding of the pharmacodynamics and mechanism of action of the chemical. Obviously, cumulative effects could be a result of an actual cumulation of chemical in the body, particularly at the target site. This is most likely for lipophilic chemicals or for those resistant to catabolism, e.g. polychlorinated biphenyls (PCBs). However, even when a chemical is rapidly catabolized, there are several mechanisms that could result in the cumulation of effects.

When a specific interaction is critical to producing the toxic effect, linearly cumulative effects would be expected simply because the probability of the interaction increases with the length of the exposure. Another mechanism could be an overloading of cellular or tissue repair functions, or of the immune system. In such cases, the cumulation of effects may not be linear with the length of the exposure. There is most evidence for such mechanisms in the case of carcinogens (Willes et al. 1985), but they may be more generally applicable.

There are several scenarios in which effects could cumulate exponentially, i.e. be synergistic with the length of exposure. An example is the case where sensitization can occur, e.g. where the effect is mediated through a secondary toxin produced by an inducible enzyme system. Another example is the irreversible inactivation of acetylcholinesterase by some pesticides so that subsequent exposure causes an enhanced effect.

The analysis is further complicated by the fact that a very short exposure can produce an effect equal in magnitude to that caused by a longer exposure, if the short exposure is during a "critical window" for manifestation of the effects. This is particularly relevant to teratogenicity studies, but could also apply in other situations. For example, a carcinogen may act only when a co-carcinogen is present.

When pharmacodynamic and mechanistic studies suggest the effects would be linearly cumulative with length of exposure, the different exposures may be equated by expressing both the human and

animal doses as the dose received over a fraction of the life cycle and comparing them on this basis, i.e.

$$\text{Lifetime-amortized dose} = \frac{\text{Dose per day x number of days exposed}}{\text{Number of days in life cycle}}$$

When the effects of a chemical do not cumulate linearly with the length of the exposure, or when there is inadequate information to determine how the effects do cumulate, it may be more appropriate to compare doses directly.

Neither of these methods of comparing dosing regimes is accurate. Other methods have been developed which may be equally valid. The validity of any methodology for comparing dosing regimes is unknown, and the errors caused by extrapolating between dosing regimes could therefore range from insignificant to absolute.

3.3 EQUATING DOSING ROUTES

Differences in the route of exposure can affect the uptake of a chemical and the way it is metabolized, and thus the dose reaching the critical site. In laboratory studies, animals are most often exposed orally. This is particularly true for chronic studies. In contrast, humans are exposed in occupational settings mainly dermally and by inhalation. Humans also, of course, experience oral exposure through food residues.

For situations in which the human risk must be extrapolated from risks to animals dosed quite differently, the error inherent in the extrapolations could be reduced by considering the dose of active toxicant (primary or secondary) reaching the "active site." Unfortunately, there are seldom sufficient data to do this. Some general corrections can be made between routes of exposure, but the generalities do not extend across classes of chemicals.

3.4 EQUATING VARIATIONS IN SENSITIVITY BETWEEN AND WITHIN SPECIES

Data suggest that some species or populations within a species are particularly sensitive to some classes of chemicals. Willes *et al.* (1985) reported that the variation in response is usually within two orders of magnitude for cancer and reproductive and acute effects. It must be emphasized that in a few cases the error has been shown to be much larger than this -- so large as to be quantal, e.g. the testing of thalidomide in rats.

Retrospective analysis of such absolute errors usually indicates that they occurred because of totally inadequate testing or because of a fundamental difference in the way the species metabolized

or took up the chemical. Only studies to enhance our understanding of toxic action could reduce the incidence of such absolute errors. Even our current knowledge allows us to detect some likely large variations.

For the majority of chemicals, a variation of less than two orders of magnitude will introduce errors that are small relative to those that arise from extrapolating to low dose levels. These errors could probably be further reduced by mechanistic and pharmacodynamic studies which elucidate the reasons that some species or populations within a species are particularly sensitive to particular classes of chemicals.

3.5 EXTRAPOLATING FROM NON-HUMAN TEST SYSTEMS TO ESTIMATE HUMAN INCIDENCE RATES

The size of the error inherent in any extrapolations depends in part on how close the estimated human dose is to the dose range at which effects were observed in animals. The middle range of a dose-response plot for observed data (10-90% response) is usually relatively well defined. However, human risk assessments are often concerned with responses at lower doses where the shape of the dose-response curve is hard to predict. There are three main zones relevant to extrapolations between doses:

(i) Within the range of the observed data. Here, errors arise mainly from intra- and interspecies variability and from observational errors in gathering data (each about 10-fold). The confidence in the extrapolations is therefore relatively high. This is the error range reflected in the 100- to 1000-fold safety factors normally applied to animal no-observed-effect levels (NOELs) when estimating "safe" human doses.

(ii) Close to the range of observed data. The dose-response curve can be extrapolated with reasonable certainty close to the observed data range. The errors are thus basically the same as described above.

(iii) Extrapolations to relatively low doses. Here, additional large errors (orders of magnitude) arise because of the uncertainties in predicting the shape of the extrapolated dose-response curve. Depending on the assumed shape of the curve at very low doses, the extrapolated risk estimate can vary by orders of magnitude.

3.5.1 Extrapolating to Low Dose Levels

Models that predict the shape of the dose-response curve can be used for low dose extrapolations. This discussion is limited to

models that predict quantal response, because these models are well developed and there are not usually adequate data for more complex models.

Comprehensive pharmacokinetic models which encompass Michaelis-Menten kinetics to allow for dose-dependent variations in the catabolism, excretion or metabolic activation of chemicals are potentially useful, but data suitable for use in such models are practically never available. When data are available, the doses can be manipulated to reflect non-linearity before they are applied to the quantal models. An example of where this would be appropriate is vinyl chloride; its metabolism to an active metabolite follows Michaelis-Menten kinetics and becomes saturated at high doses.

Models that express risk in a time and dose continuum, rather than as a simple function of dose, may be appropriate for diseases such as cancer. Again, data are usually insufficient to use such models.

There are no models that consider the differences in sensitivity between species. The quantal models fall into three categories based on the following premises:

(i) Tolerance distribution models are derived from the hypothesis that each individual has a specific tolerance to the test compound and will show no effects at exposures below this tolerance. Because there is always biological variability between individuals within a population, their tolerance levels vary. These models estimate the frequency distribution of individual tolerances over the population. Such models include the Probit, Logit and Weibull.

(ii) Stochastic models are derived from the hypothesis that a response is the result of one or more independent biological events occurring randomly. Such models include the One-hit (or linear), Multi-hit and Multi-stage.

(iii) Threshold models are derived from the hypothesis that there is a threshold dose below which a compound will cause no detectable toxic effects.

All the models usually "fit" an observed data set well, and there is thus little difference between them for predictions close to the observed data, but their predictions of incidence rates at low doses can vary by orders of magnitude (Munro and Krewski 1981; Willes et al. 1985).

Simulations using data on several compounds (Munro and Krewski 1981) indicated that extrapolations assuming sublinearity at low doses can seriously underestimate the true risk. Conversely, linear extrapolations can be excessively conservative. For most data sets it

is almost impossible to resolve the question of the shape of the dose-response curve at low doses on statistical grounds alone (Munro and Krewski 1981).

A major uncertainty for most compounds is whether or not there exists a threshold dose below which there are no detectable effects. Some toxic mechanisms suggest the existence of such a threshold (Willes et al. 1985). Although a threshold cannot be demonstrated statistically, in part because of the heterogeneity of populations and because an impractically large number of animals would be required for the study, it is conceivable that studies of toxic mechanisms could demonstrate the existence of a threshold beyond reasonable doubt, even in the absence of statistical proof. Where a threshold exists, a zero increase over background can be assumed below that value, reducing the error resulting from low dose extrapolation. Unfortunately, there are insufficient data for most compounds to predict whether a threshold is theoretically likely, much less what its value is.

The NRCC methodology for estimating risk, as discussed in Chapter 6, attempts to define the errors and uncertainties inherent to predicting human risk from non-human test systems.

4.0 GENERAL DISCUSSION OF EXPOSURE ASSESSMENT

4.1 IDENTIFYING POPULATIONS AT RISK

In any exposure assessment, it is important to identify the populations at highest risk so that their exposure levels can be estimated. Measurements of environmental levels of organic compounds are not widely available. Most often, these critical exposure groups are identified by extrapolating from other situations or by using models to predict the behavior of the chemical during and following its application.

In general, groups of the population at risk from exposure to pesticides and other industrial organic compounds can be differentiated on the basis of activities that bring them into contact with these compounds. Duration of exposure, exposure rate and predominant route(s) of absorption (inhalation, ingestion and intake through the skin) are important factors affecting exposure patterns. On this basis, there are two main groups: those exposed at work, and those exposed at home. The occupational exposure group can be subdivided according to whether exposure occurs during the production or use of the chemical. Exposure can be designated as primary, secondary or tertiary according to the level of chemical use. For example, workers manufacturing pentachlorophenol experience primary exposure; when the compound is used as a preservative by the wood industry, workers experience secondary exposure; and when the treated wood is then used, construction workers experience tertiary exposure. The general population may be exposed to pentachlorophenol by using it directly, handling treated wood or living in proximity to a production or utilization plant.

This division of exposure levels can also be applied to pesticide manufacturers and formulators, applicators and field workers. The general population can be exposed to pesticides through consumption of foodstuffs containing residues, from pick-your-own harvesting or as bystanders during pesticide application.

One person can belong to a number of these exposure groups, depending on his activities. People are exposed to many compounds at different levels, and one compound may also have several sources. Personal exposure can be affected by how much awareness the person has and by the ease with which he can avoid exposure (e.g. whether the exposure is voluntary or imposed).

4.2 ESTIMATING EXPOSURE AND DOSE

For the purposes of this document, exposure is defined as the amount of chemical which is encountered externally by the individual, and is available for uptake. Dose is the amount which enters the body and is retained, thereby becoming available to the target organs (Popendorf and Leffingwell 1982).

In making quantitative estimates of exposure to pesticides, two approaches are used: direct measurement and predictive approaches. The first includes methods that measure environmental concentrations of the chemical, as well as methods that estimate the amount actually encountered by the individual. Models based on theoretical aspects of chemical dynamics are used to make predictive estimates.

To assess possible health effects, all exposure estimates must be translated into dose to the target organ. Chemicals are absorbed from dermal, inhalation and oral exposure routes. These rates of absorption are subject to variation within the human population because of a number of parameters. The Federal Working Group on Pest Management (1974) indicated that information on the variation in the rates of absorption and metabolism of particular chemicals had generally not been developed for humans. The situation has not greatly changed to date. However, a 10- to 100-fold range can be expected based on animal data (Willes et al. 1985).

The net error associated with any method of predicting exposure and dose arises from variation in biological and behavioral factors affecting the dose received, as well as from limitations in the measurement methodology.

Human behavioral patterns can contribute to the wide ranges of exposures to pesticide residues encountered by different individuals in the same situation. Davis (1980) noted that activities performed repeatedly by the same individual resulted in fairly consistent exposure. It could be concluded, therefore, that the wide range of uptakes observed in different individuals performing the same task resulted mainly from behavioral differences. A survey of selected field studies (Wolfe et al. 1970; Durham et al. 1972; Copplestone et al. 1976; Cohen et al. 1979; Lavy, Shepard and Mattice 1980; Lavy, Shepard and Bouchard 1980; Everhart and Holt 1982; Franklin et al. 1982; Lavy et al. 1982; Maddy et al. 1982) indicated up to a 100-fold variation in uptake rates among individuals engaged in the same activity under the same experimental conditions.

Work rate and productivity may influence exposure. In an activity such as harvesting, individual productivity can be quantified in terms of the amount picked or area covered in a given time period (Popendorf and Spear 1974; Wicker and Guthrie 1980), which can in turn be related to the exposure rate. When exposure rates for strawberry harvesters were expressed per crate picked, instead of per hour, the difference between observations was reduced by half (Zweig et al. 1983). However, most behavioral variation is not as easily quantified.

The most useful sources of information for quantifying errors are reports that contain enough data to analyze the strengths and weaknesses of a study. In most cases, however, very little information is provided to validate the exposure estimates. Even when the actual

study and initial internal report are adequate, the published versions are usually so condensed that analysis is impossible.

4.2.1 Estimating Dose from Environmental Residues

Dose estimates based on extrapolations from ambient pesticide residue levels involve extensive use of empirical relationships on the rate of intake of residues from various media (e.g. air, food), as well as on the range of field residues measured.

Values for residue levels may be chosen to deliberately bias on the side of an overestimate (the worst case), or to reflect the mean with a specified distribution. Ambient residues of pesticides have been found to differ widely in a given situation, partly because of a lack of uniformity of application, and 10- to 100-fold differences have been encountered (e.g. agriculture). The number of samples analyzed in most studies is not large enough to provide a good estimate of the true average and the variability surrounding that average (Gunther 1980). In this situation, it is common to do a worst-case analysis (Gunther 1980), i.e. to use the highest residue levels, as well as to examine what appears to be the norm. The intent is to bias the error on the side of caution.

Another common practice used in estimating residue levels is to pool results from a number of sources. These data can be used to predict the norm, but may have no relevance to a specific source. For example, residue data obtained from retail food samples in which samples are pooled before they are analyzed do not reflect the variation in samples from different regions. Information on source and availability of samples from that source should be included with the data to give an indication of the precision and bias of the measurement.

Source-specific data are not generally applicable to other situations. For example, air monitoring data taken from an individual industrial plant will be specific to that situation, and give little or no idea of what would generally be encountered by workers.

The rate of oral ingestion of pesticide residues is affected in part by the rate of consumption of foods which may contain these residues. Three sources of information are available: food disappearance statistics, meal analysis and specific item analysis. Food disappearance statistics, published periodically by Statistics Canada, are based on the amounts of food which are available for consumption by the total Canadian population. These figures produce an average, but are not indicative of what is consumed by an individual or a specific group of individuals. For example, in NRCC (1981) it was calculated that the diet of the average Canadian contained only 14 g of fish per day when the total yearly consumption was averaged on a daily basis. However, in the worst case, in which someone consumed a meal of fish (120 g) every day, the intake would exceed the average by nearly an order of magnitude.

4.2.2 Estimating Dose by Personal Monitoring

Personal monitoring techniques generally involve entrapment of pesticide residues as they come into contact with the subject, or removal of retained residues at the end of an exposure period. The dermal absorption rate for the pesticide is then used to extrapolate from dermal exposure to dose. Table 4-1 describes the advantages and disadvantages of some methods currently used to measure personal exposure. The techniques are reviewed and evaluated by Durham and Wolfe (1962) and Davis (1980, 1984).

The errors associated with personal monitoring techniques are of two types. Systematic biases are errors that arise from limitations in the methodology. Individual variability includes errors introduced by biological and behavioral differences among members of the exposure group; these affect the rate of intake and the residues encountered. Some of the types of errors associated with personal monitoring techniques are described in Table 4-2. For those errors described as quantifiable, we attempt in this chapter to define the error distribution within a range.

4.2.2.1 Dermal exposure assessment.

Measurement of pesticide residues coming in contact with the skin is basically accomplished by two methods. In the first method, patches of fabric or gauze or whole garments are used to trap residues that would otherwise contact skin or clothing. Alternatively, a solvent rinse is used to remove residues from the skin, usually from the hands and forearms.

Systematic biases

Several problems are associated with the use of fabric collectors. The ability of fabrics or gauze to trap and retain residues differs from those of skin and possibly clothing. Serat et al. (1982) found that differences in cloth type or finish of dermal patches significantly changed ($p \leq 0.001$ and $p \leq 0.025$, respectively) the recovery of parathion. Knaak et al. (1978) showed that changing the fabric finish by prewashing led to 10-50% losses in the capacity of fabric to retain impinged residues. In both these studies, the amount of residues retained appeared to be within an order of magnitude when different fabrics were compared, with cotton gauze retaining the least amount of residues impinged. A comparison with the ability of residues to deposit and be retained by skin is not available; however, considering that the skin's properties differ widely from those of fabric, residues deposited and retained could differ by more than an order of magnitude.

Table 4-1. Common methods for personal monitoring of exposure to pesticide residues.

Route of exposure	Method	Description	Disadvantages	Comments
Dermal	Dermal patches (dermal exposure)	-small squares of α-cellulose absorbent paper, or layers of surgical gauze backed with an impermeable layer, are attached to clothing or placed next to the skin for collection of pesticide residues; patches are subsequently extracted and residues measured	-if pesticide is volatile or susceptible to hydrolysis or oxidation, considerable losses could occur during collection -fabrics and skin differ in ability to trap and retain residues -patches or gloves may become saturated -may contain materials which interfere with analysis, or residues may not be easily extractable from this material -often difficult to get workers to wear gloves	-α-cellulose absorbent paper patches are best used for estimation of exposure to liquid sprays; surgical gauze is best for trapping dusts, granular materials and dried residues
	Gloves (whole hands exposure)	-gloves are subsequently extracted and amount of residues measured		
	Hand rinse (whole hands exposure)	-hands are rinsed vigorously in a measured amount of solvent, usually ethanol or distilled water, to remove residues; alternatively, hands are swabbed with gauze pads wetted with solvent	-ethanol and distilled water may not be the best solvents for dissolving residues; however, they are the least irritating to skin -solvents may interfere with analysis or cause degradation	-volume of rinse and number of rinses vary between studies
Inhalation	Respirator pads	-residues are collected on gauze pads or absorbent α-cellulose paper placed in the respirator mask; pads should be protected from splashing or drift of pesticide residues	-exposure pads may become wet with exhaled moisture, which could lead to hydrolysis of susceptible compounds -pads may not be an efficient trapping medium	-advantage is that subject supplies the airflow, so that there is no need to estimate breathing rate or variation in impaction rates of particles
	Personal air monitor	-a small battery-operated pump connected to collection device is carried as close as possible to the breathing zone; trapping agents used include ethylene glycol or, more recently, solid adsorbents of resin or polyurethane foam	-airflow monitors may not detect low concentrations of residues as they cannot match human breathing rate	
Oral	No direct monitoring method available			
All routes	Urinalysis	-parent compounds and/or metabolites are measured in urine; collections are made before, during and for several days following exposure	-correlations between exposure to pesticide residues and their recovery in urine are only qualitative; insufficient information is available about excretion patterns in man to estimate absorbed dose (required information is the percentage of the compound excreted via the urinary route and percentage excreted as a particular metabolite); also, doses used to establish a standard should be in the range of those observed (as inhibition or saturation of enzyme pathways could occur at higher doses) -this method is not appropriate for lipophilic compounds with extremely slow excretion rates	-gives an estimate of exposure from all routes as absorbed dose -2,4-D is a good subject for this type of analysis because 97% is excreted in urine as the parent compound; lipophilic compounds are so slowly excreted that absorbed dose cannot be calculated this way

Table 4-2. Errors associated with personal monitoring techniques.

Monitoring method	Associated errors	Quantifiable	Comments
All techniques	Systematic biases		
	-collection efficiency	yes?	-data usually unavailable
	-analytical recovery, etc.	yes?	
	-stability of residues during storage	yes?	-data usually unavailable
	Individual variation		
	-personal productivity	yes?	-inductive estimates only
	-environmental factors	no	-see Table 4-3
	-behavioral differences	no	
Dermal patches and gloves	Systematic biases		
	-placement of patches	no	
	Individual variation		
	-residues already in clothes	no	
	-contamination of patches by touching, etc.	no	
	-workers removing gloves	no	
	-estimate of body surface area	yes	-can specify distribution and range
	-quantity of clothing worn	yes?	
	-rate of dermal absorption	yes?	-data available for few compounds
	-effects of trapping pesticide under clothing	no	-could possibly increase absorption
Skin rinse	Systematic bias		
	-efficiency of residue removal	yes	-data usually unavailable
	Individual variation		
	-absorption through skin before rinsing	no	-no data available
Respirator pads and personal air monitors	Systematic biases		
	-size spectrum of droplets	no	-affected by weather, equipment, etc.
	-airflow rate	no	-data unavailable; affects particle size spectrum
	Individual variation		
	-placement of monitor	no	-data unavailable
	-breathing rate	yes	-can specify distribution and range
Urinalysis	Systematic bias		
	-contamination of samples	no?	-usually not checked
	Individual variation		
	-variations in pharmacodynamics	?	-processes not well understood; some correction possible using standards, etc.

Although the problem of saturation has not generally been noted with the use of dermal patches, several studies (e.g. Ritcey et al. 1983; Noel et al. 1983) have observed this phenomenon when cotton gloves have served as residue collectors. A dose-dependent relationship was noted only during the first 10-15 min, after which the ability of gloves to collect residues was saturated. Because exposure of the hands is a major component of total potential exposure to pesticide residues during occupational activities (estimated 20-85%; Davis et al. 1983), the accuracy of this measurement is of great importance.

The losses of pesticide residues from dermal collectors also seem to be influenced in the field by such factors as temperature, sunlight and mechanical agitation (Serat et al. 1982). Serat et al. (1982) found the evaporative and photochemical losses of parathion were so great (30-85%) as to make the fabric patches unsuitable as collectors. Cotton gauze was found to retain only 30% of extractable parathion. It is surprising that the collection efficiency of gauze and fabric dermal collectors under field study conditions is rarely reported.

Losses during storage of samples have also been noted with both fabric collectors and solvent extracts (Davis et al. 1983). Davis et al. (1983) derived equations, based on a time scale of about 2 weeks for gauze pads and 3 months for ethanol hand rinses, that quantify the losses of residues from several types of sample. The losses were found to be dependent on the amount of time spent in storage. Although standard samples could be used to estimate storage efficiency and the exposure estimate could be corrected for losses, this is not generally done.

Because the distribution of pesticides contacting the body is not uniform, a problem arises in the use of small patches to represent a large surface area. The pattern of placement most commonly seen is the chest, top of shoulder, thigh and the back between the shoulder blades. By this placement, a thigh patch is used to estimate foot exposure, a shoulder patch to estimate head and upper arm exposure and a chest patch to measure exposure to the face. The direction and extent of bias caused by the use of a centrally located patch to represent exposure to an extremity are unknown. Durham and Wolfe (1962) recommended a total of 10 patches to adequately represent different areas of the body. To the above-mentioned placement sites, they added the front of the legs just below the knees and the back of the forearms.

The alternative to fabric collectors, i.e. rinsing residues from the skin with solvents, collects residues that actually contact the skin. The accuracy of the technique is affected by how much pesticide has been absorbed through the skin at the time of sampling. The extent of the underestimation of exposure is difficult to quantify, and depends on the interval between contact and sampling and the rate of pesticide absorption (a type of individual variation discussed in the following

section). Hand exposure estimates derived from ethanol rinses were 4-5 times smaller than estimates derived from measurements of residues on cotton or nylon gloves (Davis et al. 1983).

Individual variation

Both biological and behavioral factors contribute to the error in dermal exposure assessment methods.

A standard value for body surface area is commonly used to estimate total exposure from residues collected on gauze or fabric patches (e.g. Berkow 1931; Popendorf and Leffingwell 1982). Aside from inaccuracies in the models per se for estimating body surface area, standard values may not be representative of the exposure populations. For example, in a population of strawberry harvesters in British Columbia, up to 60% could be East Indians and 50-100% women and children. Because these individuals are smaller in weight and stature than the 50th-percentile man (Popendorf and Leffingwell 1982), and because surface area is not directly proportional to body weight, the exposure rate could be underestimated.

When individual data for height and weight are supplied (e.g. Popendorf et al. 1982; Hickey 1982), individual values for body surface area can be calculated. This offers more precision in individual exposure estimates. When height/weight data are unavailable for a heterogeneous group of individuals, a uniform distribution can be used to represent the study population.

Other sources of biological variation are the rate and extent of dermal absorption. The rate of absorption of pesticides differs not only among individuals in a population, but also according to the area of the body on which residues are received. Variation of dermal absorption with body area was up to 40-fold with hydrocortisone and 10-fold with the pesticide parathion (Maibach et al. 1971). Absorption of parathion was highest for the scrotum and forehead (100 and 36%, respectively) and lowest for the forearms, palms of hands and soles of feet (9, 12 and 14%, respectively). The extent of absorption for each area differed with the pesticide applied, as did the relative sensitivity of one area compared with another. The density of hair follicles was postulated to influence absorption rates, as was the depth of the germinal cells. This could cause variation in absorption rates between individuals as well as with body area.

Differences in behavior patterns also produce variations in the rate at which individuals are exposed to pesticides. As noted above, individuals engaged in the same activity under the same experimental conditions show a 10- to 100-fold range in exposure.

Dermal exposure is affected by the amount of body surface area covered by clothing and by the degree of penetration of pesticide residues through clothing. In exposure situations, attire can vary from a pair of shorts to coveralls, hat, gloves and respirator mask, about a ninefold variation in exposed dermal surface. The assumption that pesticide residues do not penetrate clothing is untenable. Franklin et al. (1981) used a fluorescent tracer to show that guthion pesticide spray penetrated to the skin even through rubberized clothing. Dermal patches placed under clothing have also been shown to absorb residues (Copplestone et al. 1976; Hickey 1982).

Various methods have been used to estimate the amount of pesticide contacting skin through clothing. A penetration ratio can be calculated from adjacent patches placed on top of and underneath clothing, or measurements can be taken directly from patches placed under the clothing. Maddy and co-workers (e.g. Peoples et al. 1981; Maddy et al. 1982) have used dermal patches composed of a layer of denim over a layer of gauze. Residues on the gauze represent those that would penetrate clothing to reach the skin surface. These techniques do not deal with the effects of clothing on the rate of absorption, only with the amount of residues that contact the dermal surface. It has been shown that more extensive absorption occurs when pesticide residues on skin are occluded by clothing.

Individuals may also receive dermal exposure to pesticides which is not assessed by dermal collectors. Clothing may contain biologically active pesticide residues from previous exposures even if it has been laundered (Finley et al. 1974; Easley et al. 1982). Transfer of biologically active pesticide residues from the laundry apparatus or from other clothing has also been documented (Laughlin et al. 1981). No data on the degree by which exposures are underestimated because of residues in clothing are available because of the number of unknown variables involved -- original residue content of clothing, frequency of laundering, laundering procedure used, pesticide type and formulation and fiber composition of clothing.

Dermal exposure to the hands may be underestimated by the glove technique when workers remove gloves and touch objects contaminated with pesticides. If workers touch dermal patches, exposure could be overestimated. Aside from documenting individual behavior, there is no method to quantify this type of error.

4.2.2.2 Inhalation exposure assessment.

There are two principal techniques for direct monitoring of inhaled residues (see Table 4-1). Gauze or absorbent paper placed in a respirator mask is used to trap inhaled residues, or airflow monitors are used to measure residues in the breathing zone of the subject.

Systematic biases

Sampling by either of these methods is sufficiently gross that all inhaled particulate material is trapped. However, this is not an accurate reflection of the material available for absorption through the lungs. Particles between 5 and 50 µm in diameter are deposited in the nasopharynx or high in the respiratory tract and are subsequently swallowed (Task Group on Lung Dynamics 1966; Houghton 1978). This is considered to be oral exposure (Davis et al. 1983). Popendorf and Leffingwell (1982) reported that the pesticide-containing particulate material which becomes airborne during orchard work is of such a large size that more than 95% of it would be deposited in a worker's nasopharynx. In this example, 100% of the particulate material collected by monitoring devices would be assessed as inhalation exposure, when in actual fact only 5% of the material was of a size small enough to be deeply inspired. Even of the 5% of particles deeply inspired, exhalation of two-thirds of particles between 0.1 and 0.5 µm in diameter and deposition of particles in respiratory passages other than the alveoli occur, making even smaller the percentage of airborne pesticide-containing particles that are available for absorption through the alveoli. Although absorption can still occur over the rest of the respiratory tract, these factors cause inhalation exposure to be overestimated, whereas oral exposure may be underestimated.

Another source of systematic bias is the possible hydrolysis of residues collected on respirator pads because of humidity from breathing (Davis 1980). The susceptibility to hydrolysis depends on the type of pesticide being monitored; some carbamate pesticides undergo extensive hydrolysis in the presence of humidity. Such losses could be accounted for if collection efficiency was determined using standards; however, as in the case of dermal exposure assessment (Section 4.2.2.1), little attention has been paid to this matter. The exception is a study by Durham and Wolfe (1962) in which the collection efficiency of residues on filter pads ranged from 77 to 98%, with a mean higher than 90%.

Because personal airflow monitors do not sample air that is actually breathed, systematic bias is introduced by the placement of the monitor and by the airflow rate into the monitor. The accuracy of the measurement can be improved by placing the monitor as close as possible to the breathing zone of the subject. However, the airflow rate of the monitors is generally set at 2-5 $L.min^{-1}$, whereas the adult breathing rate ranges from 6 (resting) to 60 $L.min^{-1}$ (heavy work activity). The lower airflow of the monitor could result in its sampling only the lower end of the particle size spectrum. The bias created in sampling ability has not been studied.

Individual variation

The breathing rate of a worker is required to calculate inhalation exposure rates from the concentrations of residues measured

by airflow monitors. This parameter is usually taken from the standard established for a 70-kg man involved in moderate activity (1.76 $m^3.h^{-1}$ or 29 $L.min^{-1}$; Franklin et al. 1982), with a range of possible values for the rates associated with resting to heavy activity (6-60 $L.min^{-1}$). However, breathing rate is subject to biological variation which increases with the divergence of members of the exposure population from the characteristics of the standard adult man. In a population that included a large number of women, children or people of some ethnic background, e.g. Asian, smaller size could indicate a smaller tidal volume.

4.2.2.3 Oral exposure assessment.

There is currently no standard method for monitoring oral exposure to pesticides. As discussed in Section 4.2.2.2, inhaled pesticide-containing particles more than 5 µm in diameter are deposited in the nasopharynx, where they may subsequently be swallowed and become available for absorption through the gastrointestinal (GI) tract. In this instance, absorption through the GI tract is erroneously assessed as pulmonary absorption; it accounted for 95% of inhaled residues in an example given in the previous section. Although extensive data are not available, there are indications that toxicological manifestations can be affected by the route of absorption of a chemical (Willes et al. 1985).

Oral exposure to pesticides may be further underestimated because of behavioral factors. During pesticide application and harvest, exposure could occur from licking pesticide-contaminated lips, blowing out clogged spray nozzles by mouth, touching the mouth area or smoking or eating with contaminated hands (Armstrong et al. 1973; Wolfe et al. 1974; Comer et al. 1977).

Food items and cigarettes have been analyzed for pesticide residues transferred from contaminated hands (Armstrong et al. 1973; Wolfe et al. 1974). The authors were not using this method as a routine monitoring technique, however, but rather as a way of establishing what percentage of the total exposure could be represented by the ingestion route. Because behavioral variation plays a large part in the transfer of residues from hands to mouth, the variation in oral exposure between individuals could be expected to be in the order of 10- to 100-fold (see Section 4.2.1).

Estimates for oral exposure from consumption of residues in pesticide-treated foods are discussed in Section 4.2.1.

4.2.2.4 Urinalysis.

This technique has been included under the heading of personal monitoring, even though it involves the measurement of pesticide

residues after they have been absorbed into the body. For any metabolite to be used as an index of pesticide absorption, specificity to the pesticide and dose dependence must be demonstrated (Morgan et al. 1977). Currently, reliable methodologies for the determination of phenols (organophosphates, carbamates), phenoxyacetic acids, alkyl phosphates (organophosphates) and aniline metabolites (carbamates, ureas) in urine have been developed (Shafik 1980).

The measurement of pesticide residues (either as the parent compound or its metabolites) in urine could provide a quantitative method for estimating the absorbed dose, although it has most often been used qualitatively for correlation with exposure to residues on dermal and respiratory monitoring media (Wolfe et al. 1970; Franklin et al. 1981). Possible objections to the use of urinary metabolite measurements in determining the dose of pesticides received have been enumerated by Morgan et al. (1977). Most important was the lack of information on the quantitative relationship between pesticide absorption and metabolite excretion to permit estimation of absorption from excretion.

Systematic biases in exposure estimates can arise from such methodological limitations as losses during analysis of the residues. Such biases can be compensated for using an analytical correction factor. Additionally, relating residues in the urine to the quantity retained may result in underestimation because of competing pharmacodynamic processes such as excretion by other routes, metabolism of the compound or its disposition in fatty tissue. Feldmann and Maibach (1974) found that the recovery of radioactively labeled pesticides from the urine following intravenous administration varied over a wide range (3.3-100%) for the 12 compounds tested; these included 5 organophosphates, 3 chlorinated hydrocarbons, 2 carbamates and 2 herbicides. Underestimation of dose because of pharmacodynamic processes is very low with a compound such as 2,4-D, where 95-100% (Feldmann and Maibach 1974) of the absorbed dose is excreted unchanged in the urine.

To establish the relationship between excreted metabolites and absorbed dose, Morgan et al. (1977) calculated coefficients from metabolite measurements in urine and known ingested doses of parathion, assuming 100% absorption from ingestion. However, such a quantitative relationship has not been established for urinary metabolites resulting from field exposure to pesticides. In field exposure situations, parent compounds and/or metabolites in urine samples are measured by chromatography, so that the relationship of excreted pesticide to absorbed dose is complicated by a metabolic factor.

Although similar pharmacodynamic processes could be expected within a species, individual differences in the rate and extent of pharmacodynamic processes could affect the amount of pesticide excreted in urine, and hence the precision of exposure estimates. Only a few studies have reported differences between individuals in the amounts of

metabolite or radioactive label excreted from a standardized absorbed dose (Feldmann and Maibach 1974; Morgan et al. 1977). These indicate a two- to fourfold difference. Tenfold differences in excretion of pesticide residues have been noted in field exposures of people involved in the same occupational activity (Durham et al. 1972; Lavy, Shepard and Mattice 1980; Lavy, Shepard and Bouchard 1980), but the corresponding ranges of potential exposures differed by even greater amounts. Feldmann and Maibach (1974) reported a fivefold difference between individuals for percutaneous absorption, based on previous work in which several organic chemicals were tested. This difference may be indicative of that for pharmacodynamic processes in general.

4.2.3 Extrapolating from Exposure Monitoring Data to Case Studies

Table 4-3 outlines a number of differences in exposure situations which could affect extrapolation of results from one study to another. It is necessary to closely examine the conditions in the individual studies and, ideally, to define as many variables being compared in the studies as possible. Some of the more obvious factors, such as the method of application, type of crop, overall time after application and climate, are commonly addressed in comparisons. Within an individual field study, requirements for consistency of experimental conditions are more stringent. In one study, Carmen et al. (1982) attempted to conduct exposure assessments when temperature, relative humidity and wind movement were within a narrow preselected range, and they discounted the statistical validity of results when this was not possible.

4.2.4 Predictions from Models

Estimates of exposure predicted from mathematical models can range from worst-case scenarios derived from relatively simple models to more complex computer predictions. For example, a computer simulation for predicting concentrations of pesticide drifting to the ground after aerial application (Reid and Crabbe 1980) takes into consideration such variables as type of aircraft, nozzle size, formulation, application rate, spray height and vapor pressure. The accuracy of estimates derived from models can be estimated by determining the degree of convergence with field data collected under the same conditions. This allows the relative strengths of a model to be ranked.

Simple mathematical models of worst-case exposure are outlined for dermal, inhalation and oral routes in NRCC (1982) and throughout the literature (e.g. Houghton 1978; Franklin et al. 1981). In these models, many of the variables described in computer models are bypassed by assuming that individuals are exposed to the total amount of pesticide available by that route. It is interesting to note that for aminocarb (NRCC 1982), the worst-case exposure estimate, derived from environmental residue measurements, was very close to that predicted by a more complex computer model.

Table 4-3. Factors affecting the extrapolation of data between exposure situations.

Study condition	Effects on exposure during application	Effects on exposure from environmental residues
ENVIRONMENT		
-climate		
·temperature	-could affect volatility and hence inhalation exposure -temperature inversions with still air conditions could increase exposure	-increased volatilization would result in lower foliar and soil residues and would reduce dermal exposure during harvesting, etc.
·rainfall/humidity	-size of spray particles varies with temperature and humidity; this can affect drift as well as relative importance of respiratory and oral exposure	-dislodgeable foliar residues may vary -may get saturation of wet monitoring media -residues may be present in solution rather than dust -could affect rate of hydrolysis -loss from wet soils is greater because moisture content affects absorptivity and consequently loss from volatilization, photolysis, etc.
·hours of sunlight	-photodegradation during application should be minimal	-photodegradation could affect residues and hence harvester exposure
·wind	-generally, all types of exposure would be higher in windy conditions	-less consistent placement of pesticide could increase variability in measurements
-soil type	-sorption -microbial degradation (acid/base)	-organic content of soil affects pesticide sorption -pH affects hydrolysis and microbial degradation
FORMULATION		
-liquid vs. wettable powder vs. granular	-splash from mixing liquid leads to increased dermal exposure -respiratory exposure usually lower for liquids	-dislodgeable residues generally higher with liquid formulations
APPLICATION EQUIPMENT		
-e.g. nozzle size on applicators	-affects particle size spectrum and hence influences relative importance of dermal, respiratory and oral exposure	-smaller particles more susceptible to drift
-age of equipment		
AGRICULTURAL PRACTICE		
-no. of applications	-affects total exposure	
-application rate		
-re-entry time		-re-entry time affects harvester exposure
-cultivation techniques		-irrigation could affect pesticide runoff, contamination of aquatic systems, etc.

A technique for estimating exposure and dose has been developed as part of the NRCC methodology for predicting the net cost or benefit resulting from pesticide use. As discussed in Chapter 1, this methodology is unique in that it defines the errors associated with all estimates. This is achieved by specifying ranges of values, and the type of distribution within those ranges, for all parameters input to the equations. This also permits sensitivity analysis for the parameters. The equations developed to estimate exposure and dose are described in Chapter 6.

5.0 EXPOSURE ESTIMATES FOR CASE-STUDY PESTICIDES

In this chapter, three case-study situations are analyzed to identify the populations at risk of exposure (the critical groups), to estimate the size of each of these populations and to assess the quality of data pertinent to estimating the exposure for each of these groups. Each case study is specific to an agricultural scenario and to a region of Canada. The limitations of the exposure data are discussed, and, where possible, ranges and distributions of data have been assimilated. Actual exposure estimates are made for the critical groups in each case study.

5.1 EXPOSURE TO CAPTAN RESULTING FROM ITS USE ON STRAWBERRIES IN BRITISH COLUMBIA

5.1.1 Introduction

The case study describes patterns of exposure pertaining to the use of the fungicide captan in strawberry-growing operations in British Columbia. Strawberries are also grown on a commercial basis in Nova Scotia, New Brunswick, Quebec and Ontario. Regional differences in exposure patterns could be expected on the basis of agricultural practice (e.g. application rate, method of application, spray schedule), climate and human factors pertaining to the critical population (see Table 4-3, Section 4.2.3). Because published documentation for many aspects of exposure patterns to captan was lacking, information was developed from interviews with members of the agricultural community (Patterson 1983; Peters 1983; Bean 1983).

5.1.2 Populations at Risk

The potentially significant exposure groups identified on an *ad hoc* basis by members of the agricultural community were: pesticide mixer/loaders, pesticide applicators, strawberry harvesters and consumers. Several groups with potentially high exposure were identified but not considered in the analysis because exposure could not be quantified; these groups include pesticide handlers and warehouse men, strawberry sorters, weeders and children accidentally coming into contact with high concentrations of captan during either storage or harvesting stages.

In British Columbia, farmers or members of their immediate family apparently mix, load and apply captan. Hired laborers may perform these tasks in larger operations, but in all cases the steps are usually performed by the same person (Eaton 1982; Peters 1983; Winterlin *et al.* 1984). It is unusual for farmers to possess formal certification from the B.C. Pesticide Control Branch (4% in the lower mainland region, and 5% in the Okanagan Valley). Family members and, in some cases,

hired laborers are also exempt (Eaton 1982). This lack of mandatory certification may influence awareness of the care that should be taken during the handling of pesticides.

The number of farms cultivating strawberries can be estimated by dividing the area under cultivation (1720 ha) by the area of the average farm (4-6 ha) (Peters 1983). Thus, 300-400 farm operators are at risk as a result of handling captan during application.

The size of the professional strawberry harvester population can be estimated from 1982 data (Peters 1983) as:

$$\frac{\text{Total B.C. strawberry production}}{\text{Worker productivity x crate size x length of harvest season}}$$

$$= \frac{7.7 \times 10^6 \text{ kg}}{13 \text{ crates.d}^{-1} \times 6.8 \text{ kg.crate}^{-1} \times 20\text{-}30 \text{ d}}$$

$$= 3000\text{-}4400$$

A survey of 272 farmworkers in the Fraser Valley and the Okanagan Valley (Matsqui-Abbotsford Community Services 1982) found that 61% of the farmworker population was East Indian. This group is reportedly four times as productive as other workers (Bean 1983), which may result in higher dermal exposure because of increased contact with dislodgeable pesticide residues on foliage and fruits. Differences in apparel may also influence dermal exposure; the amount of clothing worn by harvesters ranges from shorts and halter tops to several layers of clothing worn by East Indians, including long tunics and pants.

Eaton (1982), citing Canadian Farmworker's Union reports, indicated that about 70% of the East Indian farm labor force is female (as opposed to 42% of the general group; Matsqui-Abbotsford Community Services 1982), and that half of these workers take their children into the fields. Although these statistics apply for all crops, the report stated that the tendency was for children to work on soft fruit crops. If each mother brings two children into the fields, a potential group of 1300-1900 children (2 x 50% x 70% x 61% x (3000-4400)) may be exposed.

Non-professional strawberry harvesters form another exposure group that is increasing in size with the growing popularity of "pick-your-own" operations. Although the exposure period is relatively short, "naive" workers receive higher exposures than do experienced workers. For example, "pick-your-own" strawberry harvesters may be more likely to dress in shorts and sandals and to eat berries as they pick.

The general population of Canada constitutes a consumer exposure group. The range of exposures resulting from ingestion of captan residues on strawberries is influenced by consumption patterns,

which may differ according to region, age group and food preference, and by processing fresh strawberries to frozen or preserved products, which may influence the levels of residues.

5.1.3 Exposure Patterns and Levels

5.1.3.1 Mixer/applicators.

Because empirical data were not available, exposure rates for mixing and spraying were extrapolated from studies on the application of captan to other crops (Table 5-1). Variables which could influence exposure (see Table 4-3, Section 4.2.3) were adjusted to reflect the conditions of the case study wherever possible. All the studies employed direct monitoring techniques for estimation of exposure during air-blast orchard spray operations. Hickey (1982) provided the best detail of experimental conditions and design and methods of calculating exposure rates.

The following scenario for mixing, loading and applying captan is based on information provided by members of the agricultural community (see Section 5.1.1) and from the Berry Production Guide (B.C. Ministry of Agriculture and Food 1983).

Mixing

The formulation of captan most often used on strawberry crops is the 50% (ai (active ingredient)) wettable powder (captan 50 WP) mixed with water, most often in an open, 455-L (100-gallon) tank, although sometimes a 1140-L (250-gallon) tank is used. Exposure to captan is received from clouding or "puffing" of the powder as it is emptied from the bag into the mixing tank. Airborne powder could be inhaled or deposited on the skin. During this operation, farm operators reportedly wear gloves.

Application

The B.C. Berry Production Guide (B.C. Ministry of Agriculture and Food 1983) recommends application of captan at the rate of 1.7 $kg.ha^{-1}$. A Mitchell sprayer, composed of a 455-L (100-gallon) tank and a horizontal boom rig pulled behind a tractor, is generally used (Peters 1983). The sprayer has drop nozzles for application of the pesticide to the top of the strawberry plant and from the sides to get under the canopy. It is estimated that one tank load covers 0.405 ha (1 acre) in 1 h. Exposure could result from airborne spray being inhaled or landing on exposed skin area. Protective clothing usually consists of several layers, the outer layer being cotton, long-sleeved coveralls. It is unclear whether respirators are generally worn (Patterson 1983; Bean 1983).

Table 5-1. Field studies on mixing/loading and application of captan.

Study	Activity[a] (sample size)	Exposure rate ($mg.h^{-1}$) Dermal	Respired	Total	Comments
Oudbier et al. (1974)	Mixer/ loader	-	0.17±0.20 (S.D.)	-	-rates were calculated from residues found on respirator pads -based on results, respiratory exposure rate much greater for captan mixing and tank filling than for applying -were unable to adequately measure ambient air levels and therefore to determine the collection efficiency of the respirator
	Applicator		0.019±0.012		
Hansen et al. (1978)	Applicator	1.96	0.032	1.99	-emphasizes dermal exposure -calculated exposure only for sprayman, although it is stated that primary exposure came from handling the concentrated spray material while weighing and tank filling -averaged residue levels from dermal patches placed on back, shoulder and thigh to approximate exposure of face, neck and hands -assumes no exposure of skin covered with clothing
Hickey (1982)	Mixer/ loader	181 (153-hands)	5.9	187±54 (S.D.)	-calculated dermal exposure from residues on gauze patches and from ethanol hand washes -calculated penetration factors for estimating exposure through clothes; used patches placed under coveralls, adjacent to outside patches -dermal patch placement was appropriate to surface area for which exposure was estimated -assumes only one layer of clothing (may overestimate exposure as several layers are generally worn) -used Berkow's method for calculating dermal surface area, which increases representation of trunk area by a factor of 1.6 -inhalation exposure was measured with an airflow sampler in the breathing zone
	Applicator -high-volume spraying	2.6 (1.5-hands)	0.05	2.7±1.8	
	-low-volume spraying	2.3 (1.3-hands)	0.07	2.4±0.92	
McJilton et al. (1983)	Mixer/ loader/ applicator[β]	2.78	0.0045	2.78	-operators used a variety of equipment with varying tank sizes, spray pressures and captan concentrations and at varying application rates; because data were pooled, exposure rates could not be related to specific application conditions -because monitoring took place throughout loading and spraying operations, no conclusions could be made about exposure specific to each of the operations -dermal exposure measured from pads on shoulder, back and chest -exposure only for unclothed areas was considered -inhalation exposure measured from residues on pads in respirator

[a] Activities in all studies pertained to air-blast orchard spraying operations.

[β] Exposure was not differentiated by activity.

Using this scenario, exposure rates for mixer/loaders and applicators were extrapolated from the exposure rates in the study by Hickey (1982). The exposure rates for mixing/loading and for application were calculated separately, although available information indicates that both operations are performed by the same person.

For mixing/loading of captan, it was assumed that the rate of exposure was proportional to the amount loaded. Data from Hickey (1982) (Table 5-1) indicate that 24.9 kg-ai of captan 50 WP are loaded in 30 min. Thus, dermal (DER), respiratory (RER) and total (TER) exposure rates per kilogram of captan loaded can be calculated:

$$DER = \frac{0.5\ h \times 181\ mg.h^{-1}}{24.9\ kg}$$

$$= 3.6\ mg.kg^{-1}$$

$$RER = \frac{0.5\ h \times 5.9\ mg.h^{-1}}{24.9\ kg}$$

$$= 0.12\ mg.kg^{-1}$$

$$TER = \frac{0.5\ h \times (187 \pm 54)\ mg.h^{-1}}{24.9\ kg}$$

$$= 3.8 \pm 1.1\ mg.kg^{-1}$$

In the case study, one tank load covers 0.405 ha (1 acre) and the application rate is 1.7 $kg.ha^{-1}$; therefore, one tank load is 0.69 kg. Extrapolating from Hickey (1982):

$$DER = 0.69\ kg.load^{-1} \times 3.6\ mg.kg^{-1}$$
$$= 2.5\ mg.load^{-1}$$

$$RER = 0.69\ kg.load^{-1} \times 0.12\ mg.kg^{-1}$$
$$= 0.083\ mg.load^{-1}$$

$$TER = 0.69\ kg.load^{-1} \times (3.8 \pm 1.1)\ mg.kg^{-1}$$
$$= 2.6 \pm 0.76\ mg.load^{-1}$$

Daily and seasonal exposures were calculated from the number of tank loads made up and sprayed. Assuming an 8-h day, eight tank loads would be made up and sprayed daily. Seasonal exposures were calculated for five or eight sprays per season (as recommended by the B.C. Ministry of Agriculture and Food 1983), assuming a 6.1-ha (15-acre) farm which would require 15 loads to spray the entire crop once. The calculated rates for dermal, respiratory and total exposures are presented in Table 5-2.

Table 5-2. Calculated exposure rates for mixing/loading and application of captan 50 WP.

Type of exposure	Exposure (mg (mg.kg-BW^{-1}))[a]		
	Daily (8 loads)	Seasonal (5 sprays - 75 loads)	Seasonal (8 sprays - 120 loads)
Mixing/loading			
Dermal	20 (0.29)	188 (2.6)	300 (4.3)
Respiratory	0.7 (0.01)	6.2 (0.08)	10 (0.14)
Total	20.8 ± 6.1 (0.30 ± 0.09)	195 ± 57 (2.8 ± 0.8)	312 ± 91 (4.5 ± 1.3)
Application			
Dermal	1.1 (0.02)	10.5 (0.15)	16.8 (0.24)
Respiratory	0.02 (0.0003)	0.22 (0.003)	0.36 (0.005)
Total	1.1 ± 0.9 (0.016 ± 0.012)	10.5 ± 8.25 (0.15 ± 0.12)	16.8 ± 13.2 (0.24 ± 0.19)

[a] Assuming a 70-kg person.

Exposure rates for applicators were extrapolated from those in Hickey (1982), with the assumption that the exposure rate is proportional to the amount of pesticide sprayed. In Hickey (1982), for high-volume spraying, three tanks containing 3.65 kg-ai were sprayed in 1 h, giving a release rate of 11.2 kg-ai.h^{-1}. For low-volume spraying, one tank containing 13.6 kg-ai was sprayed in 1 h, giving a release rate of 13.6 kg-ai.h^{-1}. The release rates and exposure rates for high- and low-volume spraying were averaged. The error involved is probably inconsequential compared with the error generated by extrapolating from air-blast spraying to boom-rig ground spraying. Thus:

average release rate = 12.4 kg-ai.h^{-1}

DER = 2.45 mg.h^{-1} ÷ 12.4 kg-ai.h^{-1}
= 0.20 mg.kg-ai^{-1}

RER = 0.06 mg.h^{-1} ÷ 12.4 kg-ai.h^{-1}
= 0.005 mg.kg-ai^{-1}

TER = 2.6 ± 2.0 mg.h^{-1} ÷ 12.4 kg-ai.h^{-1}
= 0.21 ± 0.16 mg.kg-ai^{-1}

In the case study, 0.405 ha (1 acre) is covered with 0.68 kg captan (ai), giving a release rate of 0.68 kg-ai.h^{-1}. Extrapolating from Hickey (1982):

DER = 0.20 mg.kg-ai^{-1} x 0.68 kg-ai.h^{-1}
= 0.14 mg.h^{-1}

RER = 0.005 mg.kg-ai^{-1} x 0.68 kg-ai.h^{-1}
= 0.003 mg.h^{-1}

TER = 0.21 ± 0.16 mg.kg-ai^{-1} x 0.68 kg-ai.h^{-1}
= 0.14 ± 0.11 mg.h^{-1}

Daily and seasonal exposures were calculated assuming an 8-h day and an average farm of 6.1 ha (15 acres) (0.405 ha (1 acre) sprayed in 1 h) (Table 5-2).

The accuracy of these exposure rates was affected by conditions for which no compensation could be made because sufficient information was not available. These conditions are listed in Table 5-3 with an indication of their bias on the exposure estimate. A major drawback in extrapolating results to this case study was that none of the field studies described application of captan to low bush crops using boom-rig sprayers, but instead referred to air-blast spraying operations in orchards. Although exposure rates for mixing/loading are probably equivalent, applicator exposure could be overestimated by this method. Davis (1980) found measurable residues on dermal patches after 30-60 min for air-blast orchard spray applicators, but few quantifiable residues after 2 h for operators of tractor-drawn low-pressure boom

Table 5-3. Sources of error not accounted for in exposure estimates derived by extrapolation for mixer/loaders and applicators.

Sources of error	Bias
Extrapolation from air-blast orchard spray to ground boom-rig spray	+
Assuming no gloves worn	+
Oral exposure not included	-
Differing climatic conditions (temperature, wind, humidity)	+ or -
Differing equipment (spray pressure, nozzle size)	+ or -
Assuming 100% absorption	+
Assumed body weight	+ or -

sprayers. This suggests the overestimation for the case study may be at least a factor of two. Wolfe et al. (1967) showed that application of parathion to orchards with power air-blast sprayers results in an exposure rate over four times greater than application of spray to row crops with low-pressure boom-spray machines. However, parathion cannot be compared with captan with any degree of confidence, because its volatility is much greater.

5.1.3.2 Strawberry harvesters.

Exposure rates for this group were extrapolated from those in published studies. The most exhaustive of these studies was that of Popendorf et al. (1982), which included five field studies of strawberry harvesting operations: four in the Salinas Valley of California, and one in Corvallis, Oregon. Extensive information was supplied on experimental conditions, individual pickers (weight, age, productivity, distance covered, hours worked and exposure to residues), climate, spray schedule and captan residues in soil, air, fruit and foliage. The field study from Oregon (No. 2) was of special interest, because aspects such as growing practices, weather conditions and captan application patterns were similar to those in the British Columbia situation.

In Oregon, berries are harvested during a 3-week season in June/July, rather than from April to November as in California. Because of the short harvest season, all spraying is done in the 2 months prior to harvest, whereas in California captan is sprayed at regular intervals throughout the 8-month harvest season. There are also differences in climate, with the temperature during harvest about 5.5 C° cooler in Oregon than in the field study sites in California, and accompanied by more dew and rainfall. The differences in spray patterns and climate affect the amount of pesticide introduced to the study area, the weathering[α] of residues and consequently the levels of environmental residues. Because residue levels determine exposure (Popendorf et al. 1982; Nigg et al. 1984), the results from the Oregon field study were used in preference to California-based results for the extrapolation.

Data from a Canadian study (Ritcey et al. 1983) that measured exposure of strawberry harvesters to captan from residues accumulated on cotton gloves, sleeves and leggings were also reviewed. However, the investigators experienced problems with saturation of dosimeters in the initial 10-min exposure period. The exposure rates in Table 5-4 were obtained by expressing the raw data as exposures per 10 min and extrapolating to an hourly rate. However, the validity of this procedure as a reflection of dermal exposures is in considerable doubt,

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[α] Several climatic factors affect the disappearance of residues from the foliage of plants, and are referred to as weathering -- rainfall (washout), sunlight (photodegradation), wind (mechanical abrasion and removal), temperature (volatility) and possibly others (Hoerger and Kenaga 1972).

Table 5-4. Field studies on exposure of strawberry harvesters to captan residues.

Study	Time after application	Application rate	Environmental residues	Exposure rate: Dermal ($mg.h^{-1}$)	Exposure rate: Inhalation ($\mu g.h^{-1}$)	Comments
Popendorf et al. (1982)	Various	Various		4.7-17.4	2.7-260	- subjects monitored included children - monitoring techniques used were dermal patches, cotton gloves and air samplers - used 50th-percentile-man surface area (1.92 m^2) to determine dermal exposure (Popendorf and Leffingwell 1982) - hand and lower arm exposure constituted 81-98% of total - inhalation was not considered to constitute a significant route of exposure
(field study No. 2)	26 d	2.8 kg-ai. ha^{-1}	0.71 ± 0.32[α] $\mu g.cm^{-2}$	4.7 ± 4.1		- probably best duplicates B.C. scenario, in terms of harvesting season, temperature, rainfall and spray schedule
(field study No. 3)	3 d	2.2 kg-ai. ha^{-1}	176.3 ± 60.5[β] $\mu g.m^{-3}$	17.4 ± 14.5	176.3 ± 60.5	- only study for which individual aerosol residue data were available
Zweig et al. (1983)	4 d	4.5 kg.ha^{-1}	4.55[α] $\mu g.cm^{-2}$	39.0 ± 38.0		- measured simultaneous exposure of harvesters to captan and benomyl for strawberry operation in California - application rate seemed high; wording as to whether this was active ingredient was ambiguous - glove became wet with juice and dew; absorptive capacity may be impeded
Ritcey et al. (1983)	0-2 d	3.4 kg-ai. ha^{-1}	~20[α] $\mu g.g^{-1}$	15.0-29.4		- subjects were not professional pickers - total dermal exposure calculated as total residues on gloves, sleeves and leggings - no significant difference in residues collected on clothing was found at 10, 20 and 30 min - residues on foliage were about 10 times higher than on berries
Hickey (1982)	1-14 d	1.1 kg-ai. ha^{-1}	37-128[α] $\mu g.g^{-1}$	6.0-12.2	60-90	- exposures to apple harvesters - included for comparison because of suggestion (Popendorf et al. 1982) that transfer coefficient of foliar residues to dermal exposure is similar for hand-picked crops

[α] Dislodgeable foliar residues.

[β] Residues in aerosols.

because it assumes that skin itself does not become saturated. It should be noted that the saturation of cotton gloves could be a problem that is more widespread than is currently apparent.

Dermal exposure rates were extrapolated from the Oregon field study (Popendorf et al. 1982) (Tables 5-4 and 5-5), with the assumption that dermal exposure rates were directly proportional to the levels of dislodgeable foliar residues (DFR). Adjustments were made for application rate (AR) and postapplication interval (PAI), both of which affect the level of dislodgeable foliar residues.

To calculate worst-case exposure, levels of dislodgeable foliar residues at 2 d postapplication were assumed for the entire harvesting period. This is the minimum re-entry interval specified by the B.C. Berry Production Guide (B.C. Ministry of Agriculture and Food 1983) for captan. Values of residue levels 2 and 26 d after application were taken from the residue decay curve in the Oregon field study (Popendorf et al. 1982). An initial rapid decline in captan residues between the 1st and 3rd day after application was assumed, followed by a much slower, linear phase of decay. The general applicability of this curve is unknown.

The extrapolation was performed by the following calculation.

$$DER_{(case\ study)} = DER_{(field\ study)} \times \frac{AR_{(case\ study)}}{AR_{(field\ study)}} \times \frac{DFR_{(case\ study,\ 2\ d\ PAI)}}{DFR_{(field\ study,\ 26\ d\ PAI)}}$$

$DER_{(field\ study)} = 4.7 \pm 4.1\ mg.h^{-1}$

$AR_{(case\ study)} = 1.7\ kg\text{-}ai.ha^{-1}$

$AR_{(field\ study)} = 2.8\ kg\text{-}ai.ha^{-1}$

$DFR_{(2\ d)} = 8.02\ \mu g.cm^{-2}$

$DFR_{(26\ d)} = 0.52\ \mu g.cm^{-2}$

$$DER_{(case\ study)} = 4.7 \pm 4.1\ mg.h^{-1} \times \frac{1.7 \times 8.02}{2.8 \times 0.52}$$

$= 44.01 \pm 38.39\ mg.h^{-1}$

$= 0.80 \pm 0.70\ mg.kg\text{-}BW^{-1}.h^{-1}$, for a 55-kg person[a]

or $= 0.63 \pm 0.59\ mg.kg\text{-}BW^{-1}.h^{-1}$, for a 70-kg person

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[a] This exposure rate is a slight overestimate because exposure was calculated using surface area of standard man (1.92 m^2).

Table 5-5. Calculated exposure rates for strawberry harvesters (data after Popendorf *et al.* 1982).

Conditions	Daily (8-h) exposure ($mg.kg\text{-}BW^{-1}.d^{-1}$)	Seasonal exposure ($mg.kg\text{-}BW^{-1}$)	
		20 d	30 d
55-kg person[α]			
Dermal	6.4 ± 5.6	128 ± 112	192 ± 168
Inhalation	0.043 ± 0.015	0.86 ± 0.3	1.29 ± 0.45
70-kg person			
Dermal	5.0 ± 4.7	100 ± 80	150 ± 141
Inhalation	0.034 ± 0.012	0.68 ± 0.24	1.02 ± 0.36

[α] Exposures are slight overestimates because values were calculated using surface area of standard man (1.92 m^2).

Daily exposure rates were calculated for an 8-h day and seasonal rates for a 20- and 30-d strawberry harvest (Table 5-5). It should, however, be noted that in British Columbia many strawberry harvesters move on to pick the raspberry crop, which is sprayed with captan at the same application rate. This could result in a potential increase in exposure of 50-100%.

Aerosol concentrations of captan residues collected from personal airflow samplers were used to estimate an inhalation exposure rate (Popendorf et al. 1982; field study No. 3). The data were collected from harvesters from a California operation, and differences in climate and pesticide usage could not be accounted for.

The study gives a mean residue level for inspired aerosols as 176.3 ± 60.5 $\mu g.m^{-3}$. An assumed breathing rate of 1.7 $m^3.h^{-1}$ for moderate activity gives an inhalation exposure rate of 299 ± 103 $\mu g.h^{-1}$. To extrapolate to the case study, an adjustment was made for application rate from 2.2 to 1.7 kg-ai.ha^{-1} to give an inhalation exposure rate of:

$$299 \pm 103\ \mu g.h^{-1} \times \frac{1.7}{2.2} = 231 \pm 80\ \mu g.h^{-1}$$

$$= 5.4 \pm 1.9\ \mu g.kg\text{-}BW^{-1}.h^{-1}, \text{ for a 55-kg person}$$

$$= 4.3 \pm 1.5\ \mu g.kg\text{-}BW^{-1}.h^{-1}, \text{ for a 70-kg person}$$

Daily and seasonal rates are calculated as for dermal exposure and are presented in Table 5-5.

The ratio of dermal to inhalation exposure rates estimated for the case study seems somewhat high compared with values in other studies (Table 5-5). The estimated dermal exposure rate may be biased by using the maximum dislodgeable foliar residues in the extrapolation.

Table 5-6 indicates a number of factors not accounted for in the extrapolation, and their potential bias. The exceptional productivity of East Indian workers could affect the distribution of exposure rates within the group studied. However, Popendorf et al. (1982) investigated the possibility that saturation of deposits to the skin occurs, which would preclude a direct correlation between productivity and dermal exposure.

"Pick-your-own" harvesting operations may result in significant exposure to the general Canadian population through consumption of unwashed berries and from dermal contact with dislodgeable foliar residues. An estimate of a theoretical exposure rate for a person who picks for 1 h and eats 200-400 g of strawberries, 3 times in a season, is shown in Table 5-7. This exposure could be especially significant for children, because they would be likely to eat more of the berries and play in the foliage. Popendorf et al. (1982)

Table 5-6. Sources of error not accounted for in exposure estimates for harvesters.

Sources of error	Bias
Differing climatic conditions	+ or -
Differing spray schedule	+ or -
Differing equipment	+ or -
Oral exposure not included	-
Assumption of 100% absorption	+
Maximum level of dislodgeable foliar residues assumed	+

Table 5-7. Theoretical exposure rate for a "pick-your-own" strawberry harvester, picking for 1 h, 3 times a season.

Route	Exposure received		Assumptions
	$mg.h^{-1}$	Seasonal (x3) (mg)	
Dermal	16.4 (4.7-37.5)	49.2 (14.1-112.5)	- average of dermal exposure rates from Table 5-4 (range in parentheses)
Inhalation	0.2 (0.05-0.38)	0.6 (0.14-1.12)	- inhalation exposure rate 1% of dermal rate
Ingestion	1.5	4.5	- ingestion of 300 g of strawberries; captan residues of 5 $\mu g.g^{-1}$ (Canadian tolerance level)
Total	18.0	54.1	- total exposure by all routes

reported a dermal exposure rate of 64.7 $mg.h^{-1}$ (2.94 $mg.kg\text{-}BW^{-1}.h^{-1}$) for a 6-year-old child whom they suspected of playing in the foliage while picking. This is 10-50 times greater than dermal exposure for other pickers in the same study.

5.1.3.3 Consumers.

The general population is exposed to captan through ingestion of residues on fruit. Exposure by this route was estimated by multiplying the amount of strawberries consumed by an individual by the residue levels in the fruit (see Section 4.2.1 for a full discussion of errors in this technique). Several studies of captan residues on strawberries are presented in Table 5-8. The range of values given by the B.C. Ministry of Agriculture and Food (Waring 1982) was used in the following calculation. Even though the range is based on only five samples, it encompasses the range of residue levels found in the other studies.

Average daily consumption patterns of 3.85 $g.d^{-1}$ for fresh strawberries, 0.09 $g.d^{-1}$ for canned strawberries (fresh equivalent) and 1.34 $g.d^{-1}$ for frozen berries (fresh equivalent) were taken from Canadian domestic food disappearance figures (Statistics Canada 1979). These figures do not represent amounts actually consumed by an individual, but indicate what is available for consumption by the Canadian population. Age and geographic location are not taken into consideration. Also, this approach averages intake of strawberries on a daily basis, which works out to 5.28 g or the equivalent of one strawberry per day. Strawberries are more likely to be eaten infrequently, in larger amounts.

The fact that residues on frozen berries may not actually be the same as those on fresh berries is also not considered in the following estimates. Results from the U.S. Market Basket Survey (Painter 1979) showed that captan residues in frozen berries may be 5% of those in fresh berries. Residues in canned berries are assumed to be insignificant, as captan is degraded by heat treatment applied to fruit during processing (Elkins et al. 1972). Possible degradation products were not considered.

Exposure rates for ingested residues from fresh, frozen and canned strawberries were estimated as follows:

$$\text{amount ingested} = \text{residue level} \times \text{amount consumed}$$

$$\text{from fresh} = (0.1\text{-}3.05\ \mu g.g^{-1}) \times 3.85\ g.d^{-1}$$
$$= 0.4\text{-}11.7\ \mu g.d^{-1}$$

$$\text{from frozen} = \frac{(0.1\text{-}3.05\ \mu g.g^{-1})}{20} \times 1.34\ g.d^{-1}$$

$$= 0.007\text{-}0.2\ \mu g.d^{-1}$$

$$\text{amount ingested} = 0.4\text{-}11.9\ \mu g.d^{-1} \text{ per person}$$

Table 5-8. Captan residue levels on strawberries or products on the consumer market.

Source	No. of samples	Residues ($\mu g.g^{-1}$)	Reference	Comments
B.C. Ministry of Agriculture and Food, 1982	5	0.1-3.05	Waring (1982)	-collected from growers at roadside stands in season
Ontario Ministry of Agriculture and Food	15 14	1980 0.32 (mean) 0.76 (max.) 1981 0.87 (mean) 2.4 (max.)	Frank et al. (1982)	-berries collected that were suspected of having high levels of residues
U.S. Market Basket Survey 1977, 1978	25 37 41	fresh 1.95 (mean) 22.3 (max.) frozen 0.14 (mean) 1.10 (max.) jam/preserves 0.02 (mean) 0.31 (max.)	Painter (1979)	-market basket survey covering 12 United States metropolitan areas
Field study (Ontario)	24	0.31-2.38	Ritcey et al. (1983)	-residue levels decreased with time after application (low level taken at 14 d post-application

For purposes of comparison, in a survey of summer and winter diets in several Canadian cities, McLeod et al. (1980) estimated 0.9-1.5 µg per person per day of captan residues ingested from fruit.

The exposure from eating infrequent, large quantities of strawberries was considered in Section 5.1.3.2. An intake of 1-2 mg captan residues per meal of strawberries was estimated.

5.2 EXPOSURE TO FONOFOS RESULTING FROM ITS USE ON ONIONS IN SOUTHERN ONTARIO

5.2.1 Introduction

Fonofos, an organophosphate insecticide, is recommended for use on onions for the control of the onion maggot fly. It is extensively used in the Holland Marsh, Ontario. Fonofos is planted with the onion seed in combination with the fungicide thiram as a granular formulation (Dyfonate 5-thiram 10). Information on growing practices and operations was obtained in interviews with members of the agricultural community (Ritcey 1983; Valk 1984).

5.2.2 Populations at Risk

Because fonofos is applied into the ground with the onion seed[a], and the onions are harvested and bagged mechanically, the main exposed populations are loader/applicators and onion consumers. The size of the former group was estimated to be the number of onion growers in the Holland Marsh area, which is approximately 200 (Valk 1984). Although there are two other areas in Ontario where yellow seed onions are grown, fonofos is not used as the insecticide (Valk 1984). Onion consumers were considered to be the population of Canada. As for strawberries, exposures would be expected to vary according to patterns of consumption.

Weeding and thinning the onion crop are apparently not common, but could result in exposure of personnel to fonofos residues in the soil. These practices could become more important if a suitable substitute is not found for the herbicide currently employed, which has been taken off the market (Valk 1984). Pesticide handlers, warehouse men and children accidentally exposed were also not considered because of the lack of information on which to base exposure patterns.

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[a] The fonofos granules are loaded into a hopper at the top of the seeding apparatus, which may be set to drop them at the desired rate.

5.2.3 Exposure Patterns and Levels

5.2.3.1 Loader/applicators.

Loader/applicators may be exposed from handling the granules, contact with and inhalation of smaller particles dispersed into the air and inhalation of insecticide vaporized from the surface of the carrier.

A worst-case exposure to vaporized fonofos can be calculated as 6.7×10^{-2} mg.kg-BW^{-1}.h^{-1} for a 70-kg man with a respiration rate of 29 L.min^{-1}. The calculation uses the gas law and a vapor pressure for fonofos of 2.8×10^{-2} Pa (2.8×10^{-7} atm) at 25°C, and it assumes 100% inspiration of vaporized fonofos. This exposure pertains to a situation in which the air is saturated with fonofos, and is most appropriate to conditions resulting from a spill in an enclosed space. The estimate far exceeds the likely vapor concentration of fonofos from a 5% granular formulation used in an open field.

Exposure would, therefore, most likely result from dermal contact with and inhalation of airborne particles dispersed by air movement and during application. The most readily dispersed fraction is dust, defined as particles less than 150 µm in diameter. The extent to which dusts are formed depends on the type of granules. Other important factors which influence the extent of exposure to applicators are the capacity of the hopper (number of fillings required), the speed of application and the recommended application rate.

To date, no field studies have been found which measure exposure of applicators to fonofos. Using the available information, a worst-case estimate was made for dermal exposure (Table 5-9). The estimated daily exposure rate is 70 g.d^{-1}. This estimate seems unreasonably high, and is several orders of magnitude higher than that calculated by Lloyd and Bell (1967) using the techniques of Durham and Wolfe (1962) for operators of tractor-drawn equipment dispersing a granular pesticide formulation (40-65 mg.d^{-1}). About 4-6 mg of the residues were collected from the face, neck and hands, implying that the use of appropriate protective clothing[α] could reduce the dermal exposure to a level representing 10% of dermal surface area.

Lloyd and Bell (1967) also calculated inhalation exposure for a number of granular formulations applied in different ways. The highest inhalation exposures (0.24-0.45 mg.d^{-1}) were for 10% phorate adsorbed to attapulgite clay placed or broadcast on the crop; the lowest average inhalation exposures were for 10% thionazin adsorbed to Fuller's earth and planted in the furrow. Inhalation of 5% fonofos adsorbed to white clay, planted in the furrow, probably lies somewhere within this range.

[α] Lloyd and Bell (1967) suggested that protective clothing should be of material which readily sheds dust and of such a design that granules cannot lodge in pockets or pleats. Sleeves should be pulled over cuffs of gloves.

Table 5-9. Estimation of worst-case dermal exposure for applicators of fonofos.

Parameters used	Parameter values	Comments
Recommended application rate	1.125 kg-ai.ha^{-1}	- Ontario Ministry of Agriculture and Food (1983)
Area planted per day	2.8 ha (7 acres)	- Lloyd and Bell (1967); estimated acreage per day for applying granules to furrows while planting - assumes same application speed as in case study (similar equipment)
Fraction as dust particles	x 2.2%	- Lloyd and Bell (1967); represents fraction as dust particles for thiram/attapulgite clay; assumes fonofos/white clay to be the same - assumes uniform impregnation of fonofos so that dust contains a consistent amount - assumes dermal exposure results from contact with entire dust fraction (overestimation) - assumes no protection from clothing worn (overestimation)
Daily exposure	= 70 g.d^{-1}	
Seasonal exposure	x 1-3 = 70-210 g	- average acreage for an onion-growing operation is 4-8 ha (10-20 acres) (Valk 1984); therefore, total seasonal exposure is 1-3 times that of daily exposure

The applicability of these estimates to the case study is impossible to determine. In the one report quoted (Lloyd and Bell 1967), the application of three different organophosphate insecticides, bound to different carriers, and using methods which ranged from aerial dispersion to planting in furrows, was described. The amount of active ingredient applied was approximately the same for each insecticide tested, but the actual application rates and amounts applied were not reported. In addition, the relationship of the physical-chemical properties of fonofos and dust content of fonofos/white clay to the formulations used in the study is unknown.

5.2.3.2 Consumers.

Estimates for exposure to fonofos residues from ingestion of onions are based on the per capita food consumption statistics in Canada for 1978 (Statistics Canada 1979) and the residue levels in onions. The Statistics Canada data give a consumption of 16.83 $g.d^{-1}$ for 1977 and 17.50 $g.d^{-1}$ for 1978. These figures are not adjusted for age, geographical location or food preference, and represent the amount available for consumption rather than the amount actually consumed.

Table 5-10 summarizes studies which examine fonofos residues in onions. In a study of six farms from the Holland Marsh area using fonofos at the recommended rate of 1.1 $kg.ha^{-1}$, there were no detectable residues in onions at harvesting (Frank et al. 1982). Results from experimental plots treated with 1.1 $kg\text{-}ai.ha^{-1}$ (four replications) showed residues of 2 and 17 $\mu g.kg^{-1}$ in onions in 1978 and 1979, respectively (limits of detection were 2 and 5 $\mu g.kg^{-1}$, respectively).

Assuming a worst-case situation in which the Canadian residue tolerance limit for fonofos of 0.1 $mg.kg^{-1}$ onions (Braun et al. 1980) is found, multiplied by the average consumption rate, gives a per capita intake of 1.72 $\mu g.d^{-1}$. Because 85% of the crop is treated with fonofos (Valk 1984), the intake would be reduced to 1.5 $\mu g.d^{-1}$. Although intake is not constant on a daily basis, consumption of onions more closely follows this pattern than does consumption of fresh strawberries (see Section 5.1). Some hydrolytic degradation of fonofos may occur when onions are cooked.

5.3 EXPOSURE TO 2,4-D/2,4,5-T RESULTING FROM THEIR USE ON CONIFERS IN NEW BRUNSWICK

5.3.1 Introduction

The case study looks at the use of the herbicide mixture of 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) for conifer release in forestry plantations in New

Table 5-10. Studies listing residue levels in onions treated with fonofos.

Study	Application rate ($kg\text{-}ai.ha^{-1}$)	Soil residues ($mg.kg^{-1}$)	Onion residues ($mg.kg^{-1}$)	Comments
Khan et al. (1976)	1.1	19.3 (May) 17.4 (June) 9.3 (Sept.)	nd[a]	- yellow seed onions grown in organic soils in Quebec
	2.2	30.4 (May) 27.2 (June) 12.1 (Sept.)	nd	- results based on experimental plots
Braun et al. (1980)	2.2		0.02	- results for pickling onions based on experimental plots (Ontario)
	3.3		0.03	
	4.5		0.02	
Frank et al. (1982)	1.1	1.21 ± 0.96	nd	- results from six farms surveyed in 1978 (yellow seed onions)
	1.1		0.002, 0.017	- results for yellow seed onions in experimental plots (Ontario), 1978, 1979
	2.2		0.004, 0.025	
	4.5		0.003, 0.051	

[a] Not detected, less than $0.001\ mg.kg^{-1}$.

Brunswick. The exposure assessment focusses on occupational groups which are in direct contact with the pesticide spray, rather than with environmental residues.

The formulations used in New Brunswick contain a 50:50 mix of esters of the two phenoxyacetic acids. Formulations of both 2,4-D and 2,4,5-T have been found to contain several dioxin isomers. The 2,7-dichloro-, 1,3,7-trichloro- and 1,3,6,8- or 1,3,7,9-tetrachlorodibenzo-p-dioxin have been identified in 2,4-D. The tetra isomer, 2,3,7,8-tetrachlorodibenzo-p-dioxin, has been identified as a by-product of the manufacturing process of 2,4,5-T, although levels are now below 1 $\mu g.kg^{-1}$, the limit of detection (Cochrane et al. 1981).

5.3.2 Populations at Risk

Applicators of 2,4-D/2,4,5-T in New Brunswick constitute an exposure group. A typical spray crew using a helicopter or fixed-wing aircraft consists of a spray pilot, a spotter pilot and spotter, a ground crew of one supervisor and two or three mixer/loaders, and three people in trucks to man the 24-h block on access roads. The mixer/loaders come in contact with the concentrated product. With three major private companies involved in spraying herbicides for conifer release, an estimated 50 applicators may be involved in the spray program.

Bystanders not involved in the spray operation are usually detected by spotters and sent out of the area, so that exposure to the general population from direct spraying is minimized. However, the general population may be exposed to environmental residues from the ingestion of water, wild berries and game sprayed with 2,4-D and 2,4,5-T.

5.3.3 Exposure Patterns and Levels

5.3.3.1 Applicators.

In New Brunswick, the majority of 2,4-D/2,4,5-T is applied aerially, by helicopter or fixed-wing airplane, at an application rate of 1.68 $kg\text{-}ai.ha^{-1}$. Approximately 10-15% is applied from the ground with trucks.

J.D. Irving, the largest forestry company in New Brunswick, uses 2,4-D/2,4,5-T at a rate of about 3 $L\text{-}ai.ha^{-1}$ (17 000 L are used to cover 6000 ha of land) (Oxley 1984).

For mixing operations, the chemicals are pumped from drums into a main tank. The oil used in the formulation is then pumped in and mixed. Stirring is done externally. Helicopter tanks are loaded from the main tank with a hose inserted into the hopper and pumped like a

gasoline pump. Loading of fixed-wing aircraft differs in that the hose has a fitted coupling which clamps to the tank. No leakage or splashing would be expected from loading of aircraft. During this operation, the mixer/loader wears protective clothing consisting of a plastic suit, gloves, a respirator and goggles.

Spraying of herbicide is performed for 2 h in the morning and 2 h in the evening when the wind speed is lowest. Over a 3-week spraying session, with a 5-d workweek, mixer/loaders could potentially work with 9600 L (2100 gallons) of herbicide mixture over 210 min of loading time. These figures are calculated from the time taken to fill the spray tank and the frequency of fill-ups. Although these parameters differ for helicopters and fixed-wing aircraft because of different-sized spray tanks, the amount loaded and the duration of loading work out to the same numbers. The types of coupling on the hoses also vary and could affect exposure. Pilots of helicopters and aircraft keep the same hours as the loaders (i.e. 4 $h.d^{-1}$ for 15 d, approximately), during which time they stay inside the aircraft. Their protective clothing consists of a coverall.

Field studies compiled in Table 5-11 list exposures for a number of occupational activities under differing conditions (application rate, formulation, method of preparation, application), mostly for one exposure session. At two sessions per day for 3 weeks (~30 spray sessions), seasonal exposure could amount to 30 times the range of values in Table 5-11.

5.3.3.2 Bystanders.

In the New Brunswick scenario, the number of bystanders sprayed is minimized by the use of inanimate markers to mark spray swaths, as well as by regulations which require a setback of 8 km (5 miles) from inhabited areas. Spraying is done early in the morning and the evening to minimize wind drift. It is possible that people walking through reforestation areas (hikers, fishermen, tree-planting crews) could be exposed during spray operations if they are not detected by spotters.

In NRCC (1983), exposure of bystanders to 2,4-D at various distances from the sprayline was estimated using a computer model. At low wind speeds, the estimated bystander exposure at 8 km (5 miles) from the sprayline was negligible. For observers and bystanders at 0 and 10 m from the sprayline, exposure estimates from field studies were several orders of magnitude higher than those from the computer model. In addition to the distance from the sprayline, nozzle size and droplet spectrum are important factors in determining exposure.

5.3.3.3 General population exposure to environmental residues.

Water contamination from the use of 2,4-D/2,4,5-T near forest streams was investigated by Norris (1981), using 1960's data gathered

Table 5-11. Field studies of exposure levels from aerial application of 2,4-D or 2,4,5-T for a number of occupational groups.

Reference	Group	Application (kg-ai.ha^{-1})	Potential exposure (mg.kg-BW^{-1}) Dermal	Inhalation	Absorbed dose (urine) (mg.kg^{-1} per exposure)	Comments, limitations and biases
Lavy et al. (1982)	Pilot	2.2 (2,4-D; helicopter)	0.0005	nd[a]	0.0198	-study conducted in Washington -work crews tested in normal spray attire, taking no special precautions -2,4-D applied in diesel oil and water -denim patches were used to measure dermal exposure; placement was next to exposed skin areas, i.e. shirt, cuffs, collar and hat band
	Mechanic	"	0.0233	nd[a]	0.00585	
	Mixer/loader	"	0.0448	0.1	0.0196	
	Supervisor	"	0.0002	nd[a]	0.00231	
	Observer (20-150 m)	"	0.0001	nd[a]	0.00049	
Frank et al. (1983)	Mixer/loader 1	1.62 (2,4-D; helicopter)	-	-	0.049	-study conducted in northeastern Ontario (regenerating conifer forest) -2,4-D mixed with water -mixers 1 and 2 and supervisor were inexperienced and used new equipment; other workers were experienced and used older equipment -workers wore protective clothing (coveralls, gloves, boots, hard hats, face shields and respirators) -the bystander wore only shorts, t-shirt and sneakers
	2	"	-	-	0.0048	
	3	"	-	-	0.21	
	Supervisor	"	-	-	0.0024	
	Mixer/flagman	"	-	-	0.099	
	Flagman	"	-	-	0.067	
	Bystander	"	1.9	-	0.01	
Lavy, Shepard and Bouchard (1980)	Pilot 1[β]	2.24 (2,4,5-T; helicopter)	0.11	nd[δ]	0.005	-study conducted in south-central Arkansas -experienced workers participated; no special protective clothing was worn; normal attire was long trousers, long- or short-sleeved shirts and shoes -gauze patches pinned to chest, back and upper arms were used to measure dermal exposure -inhalation exposure was measured with a portable airflow pump
	2[γ]	"	nd	nd[δ]	0.038	
	Mixer 1	"	0.12	nd[δ]	0.065	
	2	"	0.042	nd[δ]	0.096	
	Supervisor 1	"	0.024	nd[δ]	0.004	
	2	"	nd	nd[δ]	0.003	
	Flagman 1	"	nd	nd[δ]	0.0015	
	2	"	nd	5.15	0.001	
Franklin et al. (1982)	Pilot	1.68-2.24 (2,4,5-T; fixed-wing aircraft)	0.019	6.0×10^{-3}	0.00967	-study conducted in Saskatchewan -2,4-D mixed with diesel oil -work clothing was clean cotton coveralls, shirt and pants -patches sewn to sweat bands placed under work clothing next to the body at the neck, left anterior chest, upper arms, wrists, knees and ankles, and patches located outside work clothing were also used to measure dermal exposure -inhalation exposure was measured using an airflow pump -data for some days not used because of missing patches
	Mixer	"	0.433	1.34×10^{-4}	0.0388	
	Water carrier		0.027	6.0×10^{-5}	0.00425	
Nash et al. (1982)	Pilot	360 kg-ai applied in 14 h (2,4,5-T; fixed-wing aircraft)	-	-	0.006[c]	-study conducted in eastern Washington -experienced workers participated; normal attire; precautions were followed
	Mixer/loader	585 kg-ai applied in 20 h	-	-	0.0196[c]	

[a] Not detected; limit of detection is 0.05 µg.kg-BW^{-1}.

[β] Microfoil boom.

[γ] Raindrop nozzle.

[δ] Limit of detection unknown.

[c] Amount in urine per day (not per exposure).

before untreated buffer strips were required along the edges of streams in Oregon. His findings indicated that herbicide found in stream water was the result of direct application to the water; results from the most heavily contaminated stream showed peak 2,4-D levels of 0.071 $mg.L^{-1}$, declining to 0.044 $mg.L^{-1}$ in 4.5 h. Another cause could be heavy rains immediately following application.

Norris (1981) analyzed venison tissue samples for 2,4,5-T residues from sprayed areas. At a $\leq$0.006-0.010 $mg.kg^{-1}$ detection limit, residues were found to be undetectable in all edible parts except the liver. Ingestion in 1 week of 0.45 kg (1 lb) of liver which contained the highest level detected would amount to ingestion of 0.0095 mg 2,4,5-T.

Herbicide residues on wild berries are a potential source of residues for the general population. Spraying of forestry plantations for conifer release is done between August and mid-September in New Brunswick. The major competing species are raspberry and pincherry, and ripening of their fruit overlaps this period (late July - early August; Frank et al. 1982). In New Brunswick, all access roads to sprayed areas are blocked during spraying operations, and for 24 h afterward. After this, warning signs are posted along all the entrances to the areas. This action minimizes, but does not exclude, the possibility of people ingesting sprayed berries. Raspberry is apparently one of the major competing species, and grows rapidly and extensively in cleared reforestation sites. Application of 0.8-6.0 $kg.ha^{-1}$ acid equivalent of 2,4-D during the ripe fruit stage of red raspberry resulted in initial residues of 2.6-31 $mg.kg^{-1}$, which declined to 0.1-3.3 $mg.kg^{-1}$ over a 2- to 5-week period (Frank et al. 1982). Eating 100 g of raspberries 24 h after spraying could potentially result in the ingestion of 0.3-3 mg of phenoxy herbicide residues, depending on which herbicide was applied.

6.0 USING THE NRCC METHODOLOGY TO ESTIMATE HUMAN EXPOSURE AND DISEASE INCIDENCE RATES: A CASE STUDY OF CAPTAN AS APPLIED TO STRAWBERRIES IN BRITISH COLUMBIA

The following case study is included to facilitate describing the NRCC methodology, to demonstrate its potential use for estimating human exposure to toxic chemicals and for extrapolating from toxicology studies in laboratory animals to estimate human risk and to illustrate the magnitude of the errors inherent to such procedures. As explained in Chapters 1 to 3, the methodology has many inadequacies because of deficiencies in the present state of extrapolative theories and techniques, incomplete knowledge of basic toxic mechanisms and gaps in the data bases of chemicals. Currently, the methodology is of little use for regulatory purposes.

Captan was selected for the case study because its data base is relatively complete. However, even the best data available are so inadequate that many assumptions have to be made. It is emphasized that the estimates generated here are not generally applicable and should not be quoted outside the context of this document.

6.1 THE NRCC METHODOLOGY FOR ESTIMATING HUMAN EXPOSURE AND DISEASE INCIDENCE RATES

The equations used to estimate exposure are described in Table 6-1. Table 6-2 includes a list of the basic data that are required for these calculations. Error ranges must be defined for each parameter in terms of a distribution within a specific range. The methodology utilizes Monte Carlo statistics to generate a set of possible solutions, each with an estimated probability of occurring, by random sampling from the range of values input for each parameter used in the calculations, over a number of iterations.[a] An estimated mean value with a specified error is then defined along with a distribution of exposure estimates within a specified range. The distribution of exposure estimates is used in the calculations that extrapolate from effects observed in laboratory animals to estimate human disease incidence rates.

The estimation of disease incidence rates for humans involves extrapolating from effects observed at relatively high doses in laboratory animals to predict effects at the usually lower human doses. Current data bases are usually inadequate to determine which method for extrapolating between doses is the most accurate. When a compound has a threshold dose for toxic action that is higher than the predicted human dose, the mean theoretical risk is zero, and extrapolation procedures are unnecessary.

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[a] One thousand iterations were found to be generally sufficient to ensure homogeneous sampling.

Table 6-1. Equations for estimating exposure and dose.

TOTAL EXPOSURE	= dermal exposure + inhalation exposure + oral exposure
TOTAL DOSE	= ((dermal exposure x dermal AC[a]) + (inhalation exposure x inhalation AC) + (oral exposure x oral AC)) / (weight or BSA[a])
DERMAL EXPOSURE	= main body exposure + hands exposure
MAIN BODY EXPOSURE	= ((residue on exposed body x fraction BSA exposed) / ACF[a]) + ((residue under clothes x fraction BSA clothed) / ACF)
HANDS EXPOSURE	= residue on hands / ACF
INHALATION EXPOSURE	= total residue inhaled / ACF
ORAL EXPOSURE	= (residue on food / ACF) x volume consumed

[a] BSA = body surface area; AC = absorption coefficient; ACF = analytical correction factor (specific to each analysis).

Table 6-2. Data and error ranges and assumptions used to estimate exposure to captan as used on strawberries in B.C.

Parameter	Value ($mg.d^{-1}$) (range, distribution)[α]	Analytical correction factor[β]	Source of data[γ]
Mixer/loaders			
Dermal residues on body	3.12 (±30%, uniform)	0.5-1.5	Hickey (1982)
Dermal residues on hands	17 (±30%, uniform)	0.5-1.5	Hickey (1982)
Residues inhaled	0.7 (±15%, uniform)	0.7-1.0	Hickey (1982)
Applicators			
Dermal residues on body and hands	1.12 (±30%, uniform)	0.5-1.5	Hickey (1982)
Residues inhaled	0.024 (±30%, uniform)	0.7-1.0	Hickey (1982)
Commercial harvesters			
Dermal residues on body and hands	352 (±226, normal)	0.5-1.5	Popendorf et al. (1982)
Residues inhaled	1.85 (±0.64, normal)	0.7-1.0	Popendorf et al. (1982)
Volume fruit consumed	0[δ]	-	
General			
Body weight (kg)			
- male	60-80 (normal)	-	
- female	50-70 (normal)	-	

Table 6-2. (Cont'd)

Parameter	Value ($mg.d^{-1}$) (range, distribution)[α]	Analytical correction factor[β]	Source of data[γ]
Dermal absorption coefficient (fraction)	0.1-1 (uniform)	-	
Fraction body surface area exposed[ε]	1 (±50%, uniform)	-	

[α] Ranges, distributions and analytical correction factors were estimated on the basis of a general survey of the literature and as described in Chapters 4 and 5. More precise values were used when possible.

[β] Analytical correction factors are applied to parameter values to account for analytical errors and variations.

[γ] See Section 5.1 for more details.

[δ] It is assumed that commercial harvesters do not consume a significant quantity of fruit.

[ε] The range accounts for the variation in possible penetration of residues through clothing.

The NRCC methodology permits some choice as to which extrapolation model is used. Values for incidence rates can be generated using the One-hit, Probit or Weibull models. A "mean" value may also be generated by assuming that all the predictions between the One-hit and Probit distributions have an equal probability of being correct with a uniform distribution. The equations that describe each model require constants to be estimated from the shape of the applicable dose-response curve in the range of observable data (Appendix I.0).

The NRCC methodology allows dosing schedules to be compared directly, i.e. by assuming that the human and animal doses per day are equivalent, regardless of the time period of dosing, or as lifetime-amortized doses, i.e. by comparing the human and animal doses as a fraction of the life span.

$$\text{Lifetime-amortized dose} = \frac{\text{Dose per day x number of days exposed}}{\text{Number of days in life cycle}}$$

6.2 HUMAN EXPOSURE ESTIMATES FOR CAPTAN CASE STUDY

Human exposure and dose resulting from the use of captan on strawberries in British Columbia were estimated for mixer/loader/applicators and commercial harvesters on the basis of the data presented in Chapter 5. The error ranges for each parameter used to calculate exposure and dose are based on a review of available literature (e.g. Durham and Wolfe 1962; Copplestone et al. 1976; Peoples et al. 1981; Hickey 1982; Davis et al. 1982; Serat et al. 1982). All data and assumptions inherent to the exposure estimates are documented in Table 6-2. It must be emphasized that the available data are quite limited, and some of the assumptions made may not be valid. The purpose here is only to show how the scenarios may be simulated and the types of data required. Other data and ranges, which could be equally valid, would affect the estimates. The actual estimates should thus be treated only as examples, and should not be quoted in any other context.

The estimates of exposure and dose generated using the NRCC methodology are presented in Table 6-3.[α] Mixer/loaders and applicators are considered as one group, because these activities are usually carried out by the same person (see Chapter 5). The computer estimates are similar to those estimated as described in Chapter 5 (see Appendix II.0). Some differences result from the use of the Monte Carlo approach (see Section 6.1). For example, in the absence of specific data, dermal

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[α] These estimates must not be quoted outside the context of this document. See Section 2.0.

Table 6-3. Estimated dose for captan case study.[a]

Exposure group	Estimated dose ($mg.kg\text{-}BW^{-1}.d^{-1}$)
Mixer/loader/applicator (male)	0.20 ± 0.12
Commercial harvesters	
- male	3.12 ± 3.35
- female	3.85 ± 4.02

[a] It is not known if these estimates are generally applicable because of the large number of assumptions that were necessary. They must not be quoted outside the context of this document. See Section 2.0.

absorption is considered as a uniform distribution over a specified range compared with the more simplistic worst-case assumption of 100% in Chapter 5.

The Monte Carlo approach serves to illustrate the size of the errors in the estimates. The estimates are generated as defined ranges which are generally wide. The standard deviation is usually as large as the estimated mean value.

6.3 HUMAN INCIDENCE RATE ESTIMATES FOR CAPTAN CASE STUDY

We have made no attempt to document or to critically review the toxicology data on captan. Our purpose is only to demonstrate how laboratory animal studies may be used to predict effects in humans using the NRCC methodology. This involves identifying data of adequate quality to use as an example. The criteria for using these data include the following:

(i) the adverse effect observed in the laboratory animal can be directly equated to diagnosable human disease;

(ii) a mechanism can be postulated for either a threshold or non-threshold mode of action, or both; and

(iii) dose-response data are available for at least three doses.

The toxic effect that we chose is duodenal tumors observed in mice (Table 6-4). Incidence rates for duodenal tumors were estimated for males in each human exposure group. The estimates are based on extrapolations from effects observed at relatively high doses in male CD-1 mice (Chevron Chemical 1981).

In this study we have extrapolated to humans assuming both that a threshold exists for duodenal tumors and that it does not. The choice of a threshold dose is made solely to show how the possible existence of a threshold can dramatically affect the predicted incidence rates. The assumed threshold (Table 6-4) for tumorigenicity is based on the dose below which captan is expected to be efficiently metabolized. Captan is metabolized in the gastrointestinal tract. The metabolism is pH-dependent and occurs mainly in the duodenum where the pH first becomes alkaline. Degradation of captan requires thiols, and, at high doses of captan, the supply can become saturated. At captan doses above 1000 $mg.kg\text{-}diet^{-1}$, endogenous thiols and sulfites are significantly depleted in mice, resulting in localized abnormal conditions in the intestine, i.e. increased H^+ and decreased thiols and sulfites (Chevron Chemical 1980). At doses below 134 $mg.kg\text{-}BW^{-1}$, no unmetabolized captan can be detected in rat feces (Chevron Chemical 1980). Although the data are inadequate and the analysis is highly speculative, it could be argued that there is a threshold dose below which captan will be

Table 6-4. Toxic effect chosen to be extrapolated to humans.[α]

Effect	Experimental animal	Assumptions in extrapolation[β]	Observed effective levels ($mg.kg\text{-}BW^{-1}.d^{-1}$)		Assumed threshold ($mg.kg\text{-}BW^{-1}.d^{-1}$)
			NOEL	LOEL	
Duodenal tumors	Mice	Tumor site identical in animals and humans	?	925	100[γ]

[α] Sources include Chevron Chemical (1980, 1981, 1983) (see text).

[β] There is a general assumption that sensitivity to captan is similar among species. This assumption is obviously too simplistic (see text).

[γ] Dose below which captan is expected to be efficiently and totally catabolized (see text).

completely degraded without saturating the supply of thiols, and thus a dose below which captan may not cause duodenal tumors.

All extrapolations were done assuming that the human and animal doses per day are equivalent, regardless of the time period of dosing. The incidence rate for tumors in male harvesters was also estimated on the basis of comparing the time period of dosing as a fraction of the human and animal life spans (lifetime-amortized dose). Table 6-5 documents the assumptions inherent to the incidence rate estimates. Table 6-6 lists the constants used in the dose extrapolation models. Again, it must be emphasized that the purpose of this report is to show how these extrapolations may be done and how the errors can be estimated. The predictions are not generally applicable.

Results are presented in Tables 6-7 to 6-9.[a] The error range on incidence rates estimated for each exposure group (Table 6-7) is large mainly because of the wide distribution of exposure estimates used in the simulations. The actual error in the predicted incidence rates is likely even larger. For example, variation in the shape parameters for the extrapolation models could alter the predicted incidence rates. Such variation is not unlikely, because the estimates for the shape parameters were usually based on only three data points. The use of different extrapolation models results in incidence rate estimates for duodenal tumors in male harvesters that range over four orders of magnitude (Table 6-8).

Further variation is introduced by the methods used to compare dosing regimes. Table 6-9 shows that for male harvesters the predicted duodenal tumor incidence rate is reduced by three orders of magnitude when the doses are compared on the basis of amortizing over the life cycle rather than directly.

The possibility of a threshold dose, below which an effect would not be observed, introduces a further source of variation. In the scenario simulated for captan, the assumption of a threshold drops the predicted incidence rate to zero for duodenal tumors (Table 6-7).

The possible variation in sensitivity between and within species is another source of error. Although this error is likely small relative to the dose-extrapolation errors (Willes et al. 1985), it should, if possible, be considered in any analysis. No published extrapolation model considers such variations.

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[a] These estimates must not be quoted outside the context of this document. See discussions in text (Chapters 2 and 6).

Table 6-5. Assumptions made in estimations of human incidence rates.

Direct or lifetime-amortized[α] comparison of doses
-direct comparison ignores time period of dosing
-amortized comparison assumes the following life spans: human male = 27 000 d mouse = 550 d
-amortized comparison assumes the exposure period for commercial harvesters to be 20-30 $d.a^{-1}$ and that harvesters work only one season
Choice of extrapolation model
Choice of threshold dose for toxic effects
No errors on shape parameters for extrapolation model equations

[α] Lifetime-amortized dose = $\frac{\text{dose per day x no. days dosed}}{\text{length of life cycle (d)}}$

Table 6-6. Constants (shape parameters) used in extrapolation models.[a]

Disease	One-hit	Probit	Weibull
Duodenal tumors - male mice	$\lambda = 2.7 \times 10^{-4}$	$\alpha = -6.25$ $\beta = 1.82$	$\lambda = 5.8 \times 10^{-4}$ $m = 0.89$

[a] Calculated from data in Chevron Chemical (1981). The models and definition of model constants are described in Appendix I.0.

Table 6-7. Incidence rate estimates for duodenal tumors in each exposure group (based on uniform distribution between Probit and One-hit extrapolations and directly comparing animal and human doses).[α]

Exposure group	Threshold[β] ($mg.kg\text{-}BW^{-1}.d^{-1}$)	Incidence rate[γ] (%)
Mixer/loader/applicator	No threshold	$(2.7 \pm 2.5) \times 10^{-3}$
- male	100	0
Commercial harvesters	No threshold	$(4.3 \pm 5.8) \times 10^{-2}$
- male	100	0

[α] These estimates must not be quoted outside the context of this document. See Section 2.0.

[β] See Table 6-4.

[γ] Mean ± S.D.

Table 6-8. Incidence rates estimated[α,β] for duodenal tumors in male harvesters using individual extrapolation models.

Incidence rate (%)[β,γ]		
Probit	One-hit	Weibull
$(1.1\pm6.1)\times10^{-4}$	$(8.5\pm8.9)\times10^{-2}$	0.15±0.14

α These estimates must not be quoted outside the context of this document. See Section 2.0.

β Assumes direct dose comparison and no threshold.

γ Mean ± S.D.

δ See Table 6-6.

Table 6-9. Comparison of incidence rates estimated for duodenal tumors in male harvesters when animal and human doses are amortized over the life cycle and when doses are compared directly.[α]

Dose	Incidence rate (%)[β,γ]
Direct dose	
Threshold = 100 mg.kg-BW^{-1}.d^{-1}	0
No threshold	(4.3 ± 5.8) x 10^{-2}
Amortized dose	
Threshold = 100 mg.kg-BW^{-1}.d^{-1}	0
No threshold	(4.0 ± 5.3) x 10^{-3}

[α] These estimates must not be quoted outside the context of this document. See Section 2.0.

[β] Based on uniform distribution between Probit and One-hit dose extrapolation models.

[γ] Mean ± S.D.

APPENDIX I.0

I.0 EXTRAPOLATION MODELS

The Probit Model

This is a tolerance distribution model that assumes a standard normal distribution of individual susceptibilities. The equation is:

$$P(d) = (2\pi)^{-0.5} \int_{-\infty}^{\alpha + \beta \log d} \exp(-u^2/2)\, du$$

where P(d) is the probability of response at dose d
u is the log of the variate of the normal distribution
α and β are constants defined by the basic cumulative distribution function $P = f(\alpha + \beta \log d)$.

If the incidence rates are converted to probits and plotted against log dose, then α is equal to the intercept and β is equal to the slope of the probit regression line.

The Weibull Model

This is also a tolerance distribution model. The equation is:

$$P(d) = 1 - \exp(-\lambda d^m)$$

where P(d) is the probability of response at dose d
m and λ are calculated from a regression of $\ln(\ln(1-P))^2$ vs. $\ln d$.

The intercept of this plot is $2 \ln(-\lambda)$ and the slope is $2m$.

The One-hit Model

The One-hit model is a stochastic model. It assumes that response will occur following a single hit of the target site by a biologically effective dose. The equation is:

$$P(d) = 1 - \exp(-\lambda d)$$

where P(d) is the probability of response at dose d
λ is the negative of the slope of a regression of $\ln(1-P)$ vs. d.

APPENDIX II.0

II.0 VALIDATION OF THE EXPOSURE AND RISK COMPONENTS OF THE NRCC BENEFIT-COST METHODOLOGY

As discussed in Chapter 1, the authors were unable to complete their work on this methodology because of government constraints. Parts of the methodology have therefore not been developed, verified or validated as completely as was originally planned. This appendix describes the extent to which the exposure and risk components of the methodology have been verified and validated.

II.1 VERIFICATION

Verification of the computer models for estimating exposure and risk was thorough and included:

(i) ensuring that all the equations used were correctly derived;

(ii) ensuring that the use of constants and units was consistent; and

(iii) verifying and debugging the computer code by

(a) checking that all equations and parameters are accurately represented in the code; and

(b) comparing computer estimates with manual calculations.

These checks allow a reasonable degree of confidence that the estimates generated by the computer accurately reflect the intended logic of the methodology. However, they do not show that the methodology is inherently valid.

II.2 VALIDATION

As described in Chapter 1, this methodology cannot aspire to produce realistic risk estimates unless adequate data on all parameters and understanding of all toxic mechanisms are available. However, to be of use as a tool for ranking the relative risks of chemicals, the methodology must relate consistently to reality. Ideally, validation would prove that this is the case.

As a first step in the validation of the methodology, we have examined the accuracy of the predictions for two chemicals, captan and vinyl chloride. This was done by comparing the predictions generated by the NRCC methodology with predictions from other models and with the very limited experimental and epidemiological data available. The authors acknowledge that this is far from an ideal or complete validation, but time constraints prohibited comparisons for a larger

number of chemicals, and few data are available that permit adequate comparison with the computer predictions.

II.2.1 Captan

Table II-1 shows that exposure predictions based on the NRCC methodology compare well with exposures calculated as described in Chapter 5 (NRCC calculation), for occupational exposure to captan as applied to strawberries in B.C.

The U.S. Environmental Protection Agency recently estimated exposure and risk for captan (U.S. EPA 1985). The NRCC prediction of exposure for workers applying captan to strawberries in B.C. is close (within twofold) to the U.S. EPA estimates. The higher NRCC estimates can be accounted for by the difference in the assumption made on dermal absorption. Furthermore, the EPA values apply only to application, and it has been well documented that mixing/loading usually causes the higher proportion of exposure.

Table II-2 compares risk predictions based on the NRCC methodology with estimates calculated using the EPA methodology. The EPA estimates are approximately one order of magnitude higher than the mean NRCC estimates, possibly because they are based on the linearized multi-stage model. As discussed in this monograph, risk estimates obtained using different extrapolative models can vary over several orders of magnitude. The U.S. EPA report mentions that their estimates are approximately one order of magnitude higher than estimates made by Chevron Chemical using a linear extrapolation model.

II.2.2 Vinyl chloride

Gehring et al. (1978, 1979) compared incidence rates predicted using the One-hit and Probit models with the incidence rates actually observed for angiosarcomas induced by vinyl chloride in rats. Table II-3 shows that predictions based on the NRCC methodology are close to Gehring's predictions and to the observed data. This demonstrates that the predictions based on the NRCC methodology are accurate and that, as expected, all three of the extrapolation models fit well in the range of observed data.

Gehring et al. (1978, 1979) also compiled epidemiological data on angiosarcomas induced by exposure to vinyl chloride in humans and compared these data with incidence rates predicted by extrapolating from the laboratory data at much higher doses in rats. Table II-4 shows that, using each extrapolation model, the predictions based on the NRCC methodology are close to Gehring's estimates. The predictions using the Probit and Weibull models are within one order of magnitude of the observed (epidemiology) incidence rate. The One-hit prediction is, as expected, somewhat higher. It is not clear which prediction is the more accurate, as epidemiological incidence rates are very susceptible to bias by confounding factors as described in Roberts, Curry et al. (1985).

Table II-1. Comparison of estimates for occupational exposure to captan as used on strawberries in B.C.

Exposure group	Estimated dose ($mg.kg\text{-}BW^{-1}.d^{-1}$)		
	NRCC methodology	NRCC calculation[α]	EPA[β]
Mixer/loader/ applicator	0.20 ± 0.12	0.32 ± 0.11	0.09
Harvesters			
- male	3.12 ± 3.35	5.03 ± 3.71	-
- female	3.85 ± 4.02	6.44 ± 5.61	-

[α] See Chapter 5.

[β] Estimate based on application only; assumes 1.3% dermal absorption (NRCC methodology assumes a uniform distribution from 1 to 100%).

Table II-2. Comparison of NRCC and U.S. EPA risk predictions[α], using various extrapolation models, for occupational groups exposed to captan as used on strawberries in B.C.

Exposure group (males)	Dose	Predicted incidence rate (%)				
		NRCC			U.S. EPA - Linearized multi-stage[β]	
		Probit	One-hit	Mean[ε]	Using NRCC dose	Using EPA dose
Mixer/loader/ applicator	Direct	~0	$(5.5\pm3.1)\times10^{-3}$	$(2.7\pm2.5)\times10^{-3}$	4.6×10^{-2}[γ]	2.1×10^{-2}[δ]
Harvesters	Direct	$(1.1\pm6.1)\times10^{-4}$	$(8.5\pm8.9)\times10^{-2}$	$(4.3\pm5.8)\times10^{-2}$	7.2×10^{-1}[γ]	NA
Harvesters	Lifetime-amortized	~0	$(7.7\pm7.9)\times10^{-5}$	$(4.0\pm5.3)\times10^{-5}$	6.6×10^{-4}	NA

[α] All of the above predictions assume no threshold for toxic effects.

[β] Calculated using the U.S. EPA estimated risk factor (U.S. EPA 1985), $Q_1^* = 2.3 \times 10^{-3}$ per $mg.kg\text{-}BW^{-1}.d^{-1}$.

[γ] Based on the mean dose estimated by the NRCC methodology.

[δ] Based on the U.S. EPA estimated dose of 0.09 $mg.kg^{-1}.d^{-1}$.

[ε] Based on a uniform distribution between Probit and One-hit dose extrapolation models.

Table II-3. Comparison of incidence rates predicted using One-hit and Probit models with experimental incidence rates for angiosarcomas induced by vinyl chloride in rats.[α]

	Incidence rate (%)					
	Probit		One-hit			
Dose ($\mu g.d^{-1}$)	NRCC	Gehring	NRCC	Gehring	Weibull (NRCC)	Experimental
5521	19.5	19.8	21.6	18.9	20.0	14.8
5403	18.9	19.3	21.2	18.6	19.5	21.7
5030	17.9	17.9	19.9	17.4	17.9	22
3413	11.9	12.1	14.0	12.2	11.3	11.9
2435	8.2	8.1	10.2	8.8	7.5	6.8
739	1.5	1.4	3.2	2.8	1.7	1.7

[α] Because the metabolism of vinyl chloride follows apparent Michaelis-Menten kinetics, all estimates are based on the dose expected to be metabolized (see Gehring *et al*. 1978).

Table II-4. Comparison of incidence rates (%) predicted using several methods[α] with rates observed in epidemiology studies for angiosarcomas in humans occupationally exposed to vinyl chloride.

Epidemiology[β]					Probit predictions								One-hit predictions								Weibull predictions			
					Dose A				Dose B				Dose A				Dose B				Dose A		Dose B	
			Estimated dose ($\mu g.d^{-1}$)[ε]		NRCC		Gehring		NRCC		Gehring		NRCC		Gehring		NRCC		Gehring		NRCC		NRCC	
Group	I[γ]	IR[δ]	A	B	IR	I	IR	I	IR	I	IR	I	IR	I	IR	I	IR	I	IR	I	IR	I	IR	I
4384	1	2.3×10^{-3}	60	38	8.2×10^{-3}	0.35	5.2×10^{-3}	0.2	~0	~0	~0	~0	0.26	12	0.23	10	0.17	7.4	0.14	6.3	6.6×10^{-3}	2.9	3.7×10^{-3}	1.6
2339	0	0	200	125	0.13	3.2	0.10	2.4	4.8×10^{-3}	1.1	3.5×10^{-3}	0.8	0.88	21	0.76	18	0.56	13	0.47	11	0.31	7.3	0.17	4.0
946	2	0.2	341	213	0.40	3.8	0.33	3.0	0.15	1.5	0.12	1.1	1.4	14	1.3	12	0.94	8.9	0.81	7.6	0.62	5.8	0.34	3.2
1007	2	0.1	491	306	0.78	7.9	0.68	6.8	0.33	3.3	0.26	2.7	2.1	22	1.8	19	1.3	13	1.2	12	0.10	9.9	0.54	5.4
677	0	0	631	394	1.2	8.0	1.1	7.3	0.52	3.5	0.44	3.0	2.7	18	2.4	16	1.7	12	1.5	10	1.3	9.2	0.74	5.0
324	0	0	771	481	1.7	5.4	1.5	4.9	0.75	2.4	0.64	2.1	3.3	11	2.9	9.4	2.1	6.8	1.8	5.9	1.7	5.7	0.96	3.1
9677	5	0.05			0.30	29	0.26	25	0.12	12	0.10	10	1.0	97	0.86	84	0.63	61	0.55	53	0.42	41	0.23	22

α Predictions are extrapolated from laboratory data in rats (see Gehring et al. 1978, 1979) using Probit, One-hit and Weibull models.

β Studies reviewed in Gehring et al. (1978, 1979).

γ I = Incidence.

δ IR = Incidence rate.

ε Estimated as 500 or 200 $\mu g.(8\ h)^{-1}$ x fraction of working life exposed.

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